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(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognose or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOULARD BRUNO ET AL: "Identification of a new locus for generalized epilepsy with febrile seizures plus (GEFS+) on chromosome 2q24-q33." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 5, November 1999 (1999-11), pages 1396-1400, XP002170644 ISSN: 0002-9297 the whole document ---	1-13
X	BAULAC S ET AL: "A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33." AMERICAN JOURNAL OF HUMAN GENETICS, (1999 OCT) 65 (4) 1078-85. , XP002170645 the whole document ---	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUGSLEY MICHAEL K ET AL: "Effects of bisaramil, a novel class I antiarrhythmic agent, on heart, skeletal muscle and brain Na+ channels." EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 342, no. 1, 19 January 1998 (1998-01-19), pages 93-104, XP001009949 ISSN: 0014-2999 the whole document	12,13
A	WALLACE ROBYN H ET AL: "Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel betal subunit gene SCN1B." NATURE GENETICS, vol. 19, no. 4, August 1998 (1998-08), pages 366-370, XP001009923 ISSN: 1061-4036 cited in the application the whole document	1-13
A	MALO M S ET AL: "TARGETED GENE WALKING BY LOW STRINGENCY POLYMERASE CHAIN REACTION: ASSIGNMENT OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN3A) TO CHROMOSOME 2Q24-31" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 91, no. 8, 12 April 1994 (1994-04-12), pages 2975-2979, XP002051362 ISSN: 0027-8424 the whole document	1-13
A	MALO M S ET AL: "LOCALIZATION OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN1A) TO CHROMOSOME BAND 2Q24" CYTOGENETICS AND CELL GENETICS,CH,BASEL, vol. 67, no. 3, 1994, pages 178-186, XP000603748 ISSN: 0301-0171 the whole document	1-13
A	PLUMMER NICHOLAS W ET AL: "Evolution and diversity of mammalian sodium channel genes." GENOMICS, vol. 57, no. 2, 15 April 1999 (1999-04-15), pages 323-331, XP002170646 ISSN: 0888-7543 the whole document	1-13

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06) the whole document ---	1-13
P,X	ESCAYG ANDREW ET AL: "Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2." NATURE GENETICS, vol. 24, no. 4, April 2000 (2000-04), pages 343-345, XP001009967 ISSN: 1061-4036 cited in the application the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921875 A	06-05-1999	EP 1037900 A	27-09-2000

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(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognose or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

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TITLE OF THE INVENTION

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSE OR TREAT EPILEPSY

FIELD OF THE INVENTION

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three loci mapping to chromosome 2, which show a linkage with epilepsy in patients. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA), to variations and mutations in these sequences and to the use thereof to assess, diagnose, prognose or treat epilepsy. The invention also provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders.

BACKGROUND OF THE INVENTION

Epilepsy is one of the most common neurological conditions, occurring in about 1.0% of the general population. The disease is characterised by paroxysmal abnormal electrical discharges in the brain, which lead to transient cerebral dysfunction in the form of a seizure. A seizure is considered partial when the epileptic discharge is limited to part of one brain hemisphere, or generalised when it involves both cerebral hemispheres at the onset. The current classification of the epileptic syndromes rests on two criteria: 1) seizure type which may be generalised or partial at the onset, according to clinical and EEG features; and 2) etiology, which may be idiopathic, cryptogenic and symptomatic. Symptomatic epilepsies have multiple and heterogeneous causes including

brain injury, CNS infection, migrational and metabolic disorders. In the majority (65%) of the patients with either generalised or partial epilepsy, there is no underlying cause (idiopathic) or the cause is though to be hidden or occult (cryptogenic). Also, in the idiopathic epileptic syndromes, there is no evidence of cerebral dysfunction other than the seizure, and the neurological examination is normal. There is now increasing evidence that in this latter group, genetic factors are important, especially for the idiopathic generalised epilepsy (IGE). In a recent study, Berkovic et al (1998) showed a 62% concordance rate in monozygotic twins overall for epilepsy. In this study, a higher concordance rate has been found in the generalised compared to the partial epilepsies, with 76% concordance rate for IGE. Recent studies using molecular genetic approaches have shown that many susceptibility genes for the epilepsies in human involve membrane ion channel and related proteins. These studies include the syndrome of benign familial neonatal convulsions where two loci have been identified [EBN1 on chromosome 20, the KCNQ2 gene (a potassium channel); and EBN2 on chromosome 8, the KCNQ3 gene (also a potassium channel)] (Bievert et al, 1998; Charlier et al, 1998; Singh et al, 1998), as well as autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE - chromosome 20, and the CHRNA4 gene (the neuronal nicotinic acetylcholine receptor alpha 4 subunit)] (Steinlein et al, 1995). More recently, there was a clinical description of a new syndrome (GEFS), which consisted of generalised epilepsy with febrile seizures. According to the current classification of epileptic syndrome, this syndrome would fall in the category of IGE, based on the seizure and electroencaphalographic features. However, febrile seizures were present in all probants with GEFS, and the pattern of inheritance was clearly autosomal dominant, which are not part of the usual IGE phenotype. This unique GEFS syndrome has been shown to be associated with a mutation on the beta-1 subunit of brain voltage-gated sodium channel (SCN1B) gene (Wallac et

al, 1998). In addition, three different groups, including the group of the present inventors, have identified another locus on chromosome 2 in large kindred with this specific syndrome (GEFS). This region contains many candidate genes, including a cluster of alpha subunits of sodium channels (SCNA). Voltage-gated sodium channels play an important role in the generation of action potential in nerve cells and muscle. The alpha subunit (SCNA) is the main component of the channel, and would be sufficient to generate an efficient channel when expressed in cells *in vitro*. In turn, the beta-1 and 2 subunits need an alpha subunit to give an effective channel. The role of these subunits would be to modifiy the kinetic properties of the channel, mainly by fast inactivation of the sodium currents. The mutation found in the GEFS syndrome on the SCN1B gene was shown to reduce the fast inactivation of the sodium channels as compared to a normal SCNB1, when co-expressed with an alpha subunit. It is probable that this could be the mechanism by which the mutation induce an hyperexcitability state in the brain, leading to seizure in humans. Interestingly, the mechanism of action of most of the anticonvulsant drugs is through a reduction of the repetitive firing of neurons, which is also known to be dependent on fast inactivation. These finding make it likely that additional epilepsy genes will be identified by mutations in ion channels.

There thus remains a need to identify whether IGE is caused by a mutation in a sodium channel (SCNA). There also remains a need to assess whether a mutation(s) in SCNA is associated with GEFs. There also remains a need to determine whether a mutation that affects the fast inactivation of a sodium channel, given the particular phenotype of GEFS or IGE, could be linked to a region which includes SCNA genes.

The present invention seeks to meet these and other needs.

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

In one embodiment, the present invention relates to a genetic assay for determining predisposition to epilepsy.

In another embodiment, the present invention relates to a use of at least one of the loci of the present invention or an equivalent thereof (e.g. a loci in linkage disequilibrium therewith) as a marker for epilepsy and to determine the optimal treatment thereof (e.g. to guide the treatment modalities, thereby optimizing treatment to a particular clinical situation).

Yet in another embodiment, the present invention relates to an assay to screen for drugs for the treatment and/or prevention of epilepsy. In a particular embodiment, such assays can be designed using cells from patients having a known genotype at one of the loci of the present invention. These cells harboring recombinant vectors can enable an assessment of the functionality of the SCN1A, and/or SCN2A and/or SCN3A and a combination thereof. Non-limiting examples of assays that could be used in accordance with the present invention include *cis-trans* assays similar to those described in U.S.P. 4,981,784.

It shall be understood that the determination of allelic variations in at least one of the loci of the present invention can be combined to the determination of allelic variation in other gene/markers linked to a predisposition to epilepsy. This combination of genotype analyses could lead to better diagnosis programs and/or treatment of epilepsy. Non-limiting examples of such markers include SCN1B, EBN1, KCNQ2, EBN2, KCNQ3, ADNFLE and CHRNA4.

In accordance with the present invention, there is therefore provided a method of determining an individual's predisposition to epilepsy, which comprises determining the genotype of at least one locus selected from the group consisting of SCN1A, SCN2A and SCN3A. In one particular embodiment, the present invention provides a method of determining an individual's predisposition to epilepsy, which comprises determining a polymorphism (directly or indirectly by linkage disequilibrium) in a biological sample of an individual and analyzing the allelic variation in at least one of the loci selected from SCN1A, SCN2A and SCN3A, thereby determining an individual's predisposition to epilepsy.

In accordance with the present invention, there is also provided a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

Also provided within the present invention is a compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene, wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

SCN1A, SCN2A and SCN3A refers to genes and proteins for Sodium Channel, Neuronal Type I, Alpha Subunit isoforms, and are described at OMIM # 182389 (Online Mendelian Inheritance in Man). These genes are structurally distinct sodium channel alpha-subunit isoforms in brain, also known as brain types I, II and III, respectively. Gene, cDNA and protein sequences for the various isoforms are shown in SEQ ID NOS:1-98.

Numerous methods for determining a genotype are known and available to the skilled artisan. All these genotype determination methods are within the scope of the present invention. In a particular embodiment of a method of the present invention, the determination of the genotype comprises an amplification of a segment of one of the loci selected from the group consisting of SCN1A, SCN2A and SCN3A and in a particularly preferred embodiment, the amplification is carried out using polymerase chain reaction.

In a particular embodiment, a pair of primers is designed to specifically amplify a segment of one of the markers of the present invention. This pair of primers is preferably derived from a nucleic acid sequence of SCN1A, SCN2A or SCN3A or from sequences flanking these genes, to amplify a segment of SCN1A, SCN2A or SCN3A (or to amplify a segment of a loci in linkage disequilibrium with at least one of the loci of the present invention). While a number of primers are exemplified herein, other primer pairs can be designed, using the sequences of the SCN1A, SCN2A and SCN3A nucleic acids molecules described hereinbelow. The same would apply to primer pairs from loci in linkage disequilibrium with the markers of the present invention.

Restriction fragment length polymorphisms can be used to determine polymorphisms at the SCN1A, SCN2A and SCN3A loci (and equivalent loci).

While human SCN1A, SCN2A and SCN3A are preferred sequences (nucleic acid and proteins) in accordance with the present invention, the invention should not be so limited. Indeed, in view of the significant conservation of these genes throughout evolution, sequences from different species, and preferably mammalian species, could be used in the assays of the present invention. One non-limiting example is the rat SCN1A ortholog gene which shows 95% identity with the human SCN1A gene. The significant conservation of the mouse SCN1A gene can also be observed in OMIM (see above).

In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are provided hereinbelow.

As used herein the term "RFLP" refers to restriction fragment length polymorphism.

The terms "polymorphism", "DNA polymorphism" and the like, refer to any sequence in the human genome which exists in more than one version or variant in the population.

The term "linkage disequilibrium" refers to any degree of non-random genetic association between one or more allele(s) of two different polymorphic DNA sequences, that is due to the physical proximity of the two loci. Linkage disequilibrium is present when two DNA segments that are very close to each other on a given chromosome will tend to remain unseparated for several generations with the consequence that alleles of a DNA polymorphism (or marker) in one segment will show a non-random association with the alleles of a different DNA polymorphism (or marker) located in the other DNA segment nearby. Hence, testing of a marker in linkage desiquilibrium with the polymorphisms of the present invention at the SCN1A, SCN2A and/or SCN3A genes (indirect testing), will give almost the same information as

testing for the SCN1A, SCN2A and SCN3A polymorphisms directly. This situation is encountered throughout the human genome when two DNA polymorphisms that are very close to each other are studied. Linkage disequilibriums are well known in the art and various degrees of linkage disequilibrium can be encountered between two genetic markers so that some are more closely associated than others.

It shall be recognized by the person skilled in the art to which the present invention pertains, that since some of the polymorphisms or mutations herein identified in the SCN1A, SCN2A and/or SCN3A genes can be within the coding region of the genes and therefore expressed, that the present invention should not be limited to the identification of the polymorphisms/mutations at the DNA level (whether on genomic DNA, amplified DNA, cDNA, or the like). Indeed, the herein-identified polymorphisms and/or mutations could be detected at the mRNA or protein level. Such detections of polymorphism identification on mRNA or protein are known in the art. Non-limiting examples include detection based on oligos designed to hybridize to mRNA or ligands such as antibodies which are specific to the encoded polymorphism (i.e. specific to the protein fragment encoded by the distinct polymorphisms).

Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission.

Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell cultures, infection, molecular biology methods and the like are common methods

used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al. (1989, Molecular Cloning- A Laboratory Manual, Cold Spring Harbor Laboratories) and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York).

The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

As used herein, "nucleic acid molecule", refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (i.e. genomic DNA, cDNA, RNA molecules (i.e. mRNA) and chimeras of DNA and RNA. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or single-stranded (coding strand or non-coding strand [antisense]).

The term "recombinant DNA" as known in the art refers to a DNA molecule resulting from the joining of DNA segments. This is often referred to as genetic engineering.

The term "DNA segment", is used herein, to refer to a DNA molecule comprising a linear stretch or sequence of nucleotides. This sequence when read in accordance with the genetic code, can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

The terminology "amplification pair" refers herein to a pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. Other types of amplification processes include ligase chain reaction, strand displacement amplification, or nucleic acid sequence-based amplification, as explained

in greater detail below. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

The nucleic acid (i.e. DNA, RNA or chimeras thereof) for practicing the present invention may be obtained according to well known methods.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed. In general, the oligonucleotide probes or primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the melting point of hydrizidation thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular Cloning -A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

The term "DNA" molecule or sequence (as well as sometimes the term "oligonucleotide") refers to a molecule comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). Sometimes, in a double-stranded form, it can comprise or include a "regulatory element" according to the present invention, as the term is defined herein. The term "oligonucleotide" or "DNA" can be found in linear DNA molecules or fragments, viruses, plasmids, vectors, chromosomes or synthetically derived DNA. As used herein, particular double-stranded DNA sequences may be described according to the normal convention of giving only the sequence in the 5' to 3' direction. Of

course, as very well-known, DNA molecules or sequences are often in single stranded form.

"Nucleic acid hybridization" refers generally to the hybridization of two single-stranded nucleic acid molecules having complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred to above (Sambrook et al., 1989, *supra* and Ausubel et al., 1989, *supra*) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter, as for example in the well known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at 65°C with a labeled probe in a solution containing 50% formamide, high salt (5 x SSC or 5 x SSPE), 5 x Denhardt's solution, 1% SDS, and 100 µg/ml denatured carrier DNA (i.e. salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2 x SSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The selected temperature is based on the melting temperature (Tm) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al.,1989, *supra*).

Probes of the invention can be utilized with naturally occurring sugar-phosphate backbones as well as modified backbones including phosphorothioates, dithionates, alkyl phosphonates and α-nucleotides and the like. Modified sugar-phosphate backbones are generally taught by Miller, 1988, Ann. Reports Med. Chem. 23:295 and Moran et al., 1987, Nucleic Acids Res., 14:5019. Probes of the invention

can be constructed of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and preferably of DNA.

The types of detection methods in which probes can be used include Southern blots (DNA detection), dot or slot blots (DNA, RNA), and Northern blots (RNA detection). Although less preferred, labeled proteins could also be used to detect a particular nucleic acid sequence to which it binds. More recently, PNAs have been described (Nielsen et al. 1999, Current Opin. Biotechnol. 10:71-75). PNAs could also be used to detect the polymorphisms of the present invention. Other detection methods include kits containing probes on a dipstick setup and the like.

Although the present invention is not specifically dependent on the use of a label for the detection of a particular nucleic acid sequence, such a label might be beneficial, by increasing the sensitivity of the detection. Furthermore, it enables automation. Probes can be labeled according to numerous well known methods (Sambrook et al., 1989, supra). Non-limiting examples of labels include ^{3}H, ^{14}C, ^{32}P, and ^{35}S. Non-limiting examples of detectable markers include ligands, fluorophores, chemiluminescent agents, enzymes, and antibodies. Other detectable markers for use with probes, which can enable an increase in sensitivity of the method of the invention, include biotin and radionucleotides. It will become evident to the person of ordinary skill that the choice of a particular label dictates the manner in which it is bound to the probe.

As commonly known, radioactive nucleotides can be incorporated into probes of the invention by several methods. Non-limiting examples thereof include kinasing the 5' ends of the probes using gamma ^{32}P ATP and polynucleotide kinase, using the Klenow fragment of Pol I of *E. coli* in the presence of radioactive dNTP (i.e. uniformly lab led DNA

probe using random oligonucleotide primers in low-melt gels), using the SP6/T7 system to transcribe a DNA segment in the presence of one or more radioactive NTP, and the like.

As used herein, "oligonucleotides" or "oligos" define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthetised chemically or derived by cloning according to well known methods.

As used herein, a "primer" defines an oligonucleotide which is capable of annealing to a target sequence, thereby creating a double stranded region which can serve as an initiation point for nucleic acid synthesis under suitable conditions.

Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods. See generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25. Numerous amplification techniques have been described and can be readily adapted to suit particular needs of a person of ordinary skill. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the Q-beta replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, *supra*). Preferably, amplification will be carried out using PCR.

Polymerase chain reaction (PCR) is carried out in accordance with known techniques. See, e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; and 4,965,188 (the disclosures of all three U.S. Patent are incorporated herein by reference). In general, PCR involves, a

treatment of a nucleic acid sample (e.g., in the presence of a heat stable DNA polymerase) under hybridizing conditions, with one oligonucleotide primer for each strand of the specific sequence to be detected. An extension product of each primer which is synthesized is complementary to each of the two nucleic acid strands, with the primers sufficiently complementary to each strand of the specific sequence to hybridize therewith. The extension product synthesized from each primer can also serve as a template for further synthesis of extension products using the same primers. Following a sufficient number of rounds of synthesis of extension products, the sample is analysed to assess whether the sequence or sequences to be detected are present. Detection of the amplified sequence may be carried out by visualization following EtBr staining of the DNA following gel electrophores, or using a detectable label in accordance with known techniques, and the like. For a review on PCR techniques (see PCR Protocols, A Guide to Methods and Amplifications, Michael et al. Eds, Acad. Press, 1990).

Ligase chain reaction (LCR) is carried out in accordance with known techniques (Weiss, 1991, Science 254:1292). Adaptation of the protocol to meet the desired needs can be carried out by a person of ordinary skill. Strand displacement amplification (SDA) is also carried out in accordance with known techniques or adaptations thereof to meet the particular needs (Walker et al., 1992, Proc. Natl. Acad. Sci. USA 89:392-396; and ibid., 1992, Nucleic Acids Res. 20:1691-1696).

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific amino acid sequence thereby giving rise to a specific polypeptide or protein. It will be readily recognized by the person of ordinary skill, that the nucleic

acid sequence of the present invention can be incorporated into anyone of numerous established kit formats which are well known in the art.

A "heterologous" (i.e. a heterologous gene) region of a DNA molecule is a subsegment of DNA within a larger segment that is not found in association therewith in nature. The term "heterologous" can be similarly used to define two polypeptidic segments not joined together in nature. Non-limiting examples of heterologous genes include reporter genes such as luciferase, chloramphenicol acetyl transferase, beta-galactosidase, and the like which can be juxtaposed or joined to heterologous control regions or to heterologous polypeptides.

The term "vector" is commonly known in the art and defines a plasmid DNA, phage DNA, viral DNA and the like, which can serve as a DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

The term "expression" defines the process by which a gene is transcribed into mRNA (transcription), the mRNA is then being translated (translation) into one polypeptide (or protein) or more.

The terminology "expression vector" defines a vector or vehicle as described above but designed to enable the expression of an inserted sequence following transformation into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. The placing of a cloned gene under such control sequences is often refered to as being operably linked to control elements or sequences.

Operably linked sequences may also include two segments that are transcribed onto the same RNA transcript. Thus, two sequences, such as a promoter and a "reporter sequence" are operably linked if transcription commencing in the promoter will produce an RNA transcript of the reporter sequence. In order to be "operably linked" it is

not necessary that two sequences be immediately adjacent to one another.

Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

Prokaryotic expressions are useful for the preparation of large quantities of the protein encoded by the DNA sequence of interest. This protein can be purified according to standard protocols that take advantage of the intrinsic properties thereof, such as size and charge (i.e. SDS gel electrophoresis, gel filtration, centrifugation, ion exchange chromatography...). In addition, the protein of interest can be purified via affinity chromatography using polyclonal or monoclonal antibodies. The purified protein can be used for therapeutic applications.

The DNA construct can be a vector comprising a promoter that is operably linked to an oligonucleotide sequence of the present invention, which is in turn, operably linked to a heterologous gene, such as the gene for the luciferase reporter molecule. "Promoter" refers to a DNA regulatory region capable of binding directly or indirectly to RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of the present invention, the promoter is bound at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter will be found a transcription initiation site (conveniently defined by mapping with S1 nuclease), as well as protein binding domains (consensus sequences) responsible for the

binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boses and "CCAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

In accordance with one embodiment of the present invention, an expression vector can be constructed to assess the functionality of specific alleles of the SCN1A, SCN2A and SCN3A sodium channels. Non-limiting examples of such expression vectors include a vector comprising the nucleic acid sequence encoding one of the sodium channels (or part thereof) according to the present invention. These vectors can be transfected in cells. The sequences of the alpha subunit of the sodium channels in accordance with the present invention and their structure-function relationship could be assessed by a number of methods known to the skilled artisan. One non-limiting example includes the use of cells expressing the β-1 and β-2 subunits and the sequence of an alpha subunit in accordance with the present invention. For example, an alpha subunit having a mutation, which is linked to epilepsy, could be compared to a sequence devoid of that mutation, as a control. In such cells, the functionality of the sodium channel could be tested as known to the skilled artisan and these cells could be used to screen for agents which could modulate the activity of the sodium channel. For example, agents could be tested and selected, which would reduce the hyperexcitability state of the sodium channel (e.g. their reduction in fast inactivation). Agents known to the person of ordinary skill as affecting other sodium channels could be tested, for example, separately or in batches. Of course, it will be understood that the SCN1A, SCN2A and/or SCN3A genes expressed by these cells can be modified at will (e.g. by *in vitro* mutagenesis or the like).

As used herein, the designation "functional derivative" denotes, in the context of a functional derivative of a sequence whether a

nucleic acid or amino acid sequence, a molecule that retains a biological activity (either function or structural; e.g. sodium channel function or structure) that is substantially similar to that of the original sequence. This functional derivative or equivalent may be a natural derivative or may be prepared synthetically. Such derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved. The same applies to derivatives of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained. When relating to a protein sequence, the substituting amino acid generally has chemico-physical properties which are similar to that of the substituted amino acid. The similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophylicity and the like. The term "functional derivatives" is intended to include "fragments", "segments", "variants", "analogs" or "chemical derivatives" of the subject matter of the present invention. The genetic code, the chemico-physical characteristics of amino acids and teachings relating to conservative vs. non-conservative mutations are well-known in the art. Non-limiting examples of textbooks teaching such information are Stryer, Biochemistry, 3rd ed.; and Lehninger, Biochemistry, 3rd ed. The functional derivatives of the present invention can be synthesized chemically or produced through recombinant DNA technology. all these methods are well known in the art.

The term "variant" refers herein to a protein or nucleic acid molecule which is substantially similar in structure and biological activity to the protein or nucleic acid of the present invention.

As used herein, "chemical derivatives" is meant to cover additional chemical moieties not normally part of the subject matter of the invention. Such moieties could affect the physico-chemical

characteristic of the derivative (i.e. solubility, absorption, half life, decrease of toxicity and the like). Such moieties are examplified in Remington's Pharmaceutical Sciences (1980). Methods of coupling these chemical-physical moieties to a polypeptide or nucleic acid sequence are well known in the art.

The term "allele" defines an alternative form of a gene which occupies a given locus on a chromosome.

As commonly known, a "mutation" is a detectable change in the genetic material which can be transmitted to a daughter cell. As well known, a mutation can be, for example, a detectable change in one or more deoxyribonucleotide. For example, nucleotides can be added, deleted, substituted for, inverted, or transposed to a new position. Spontaneous mutations and experimentally induced mutations exist. The result of a mutations of nucleic acid molecule is a mutant nucleic acid molecule. A mutant polypeptide can be encoded from this mutant nucleic acid molecule.

As used herein, the term "purified" refers to a molecule having been separated from a cellular component. Thus, for example, a "purified protein" has been purified to a level not found in nature. A "substantially pure" molecule is a molecule that is lacking in all other cellular components.

As used herein, "SCNA biological activity" refers to any detectable biological activity of SCN1A, SCN2A or SCN3A gene or protein (herein sometimes collectively called SCNA genes or SCNA proteins). This includes any physiological function attributable to an SCNA gene or protein. It can include the specific biological activity of SCNA proteins which is efflux of sodium or related ions. This includes measurement of channel properties such as, but not limited to: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels, 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. At a larger scale, SCNA biological activity includes transmission of impulses through cells, wherein changes in transmission characteristics caused by modulators of SCNA proteins can be identified. Non-limiting examples of such measurements of these biological activities may be made directly or indirectly, such as through the transient accumulation of ions in a cell, dynamics of membrane depolarization, etc. SCNA biological activity is not limited, however, to these most important biological activities herein identified. Biological activities may also include simple binding or pKa analysis of SCNA with compounds, substrates, interacting proteins, and the like. For example, by measuring the effect of a test compound on its ability to increase or inhibit such SCNA binding or interaction is measuring a biological activity of SCNA according to this invention. SCNA biological activity includes any standard biochemical measurement of SCNA such as conformational changes, phosphorylation status or any other feature of the protein that can be measured with techniques known in the art. Finally, SCNA biological activity also includes activities related to SCNA gene transcription or translation, or any biological activities of such transcripts or translation products.

As used herein, the terms "molecule", "compound", "agent" or "ligand" are used interchangeably and broadly to refer to natural, synthetic or semi-synthetic molecules or compounds. The term "molecule" therefore denotes for example chemicals, macromolecules, cell or tissue extracts (from plants or animals) and the like. Non limiting examples of molecules include nucleic acid molecules, peptides, ligands (including, for example, antibodies and carbohydrates) and pharmaceutical agents. The agents can be selected and screened by a

variety of means including random screening, rational selection and by rational design using for example protein or ligand modelling methods such as computer modelling. The terms "rationally selected" or "rationally designed" are meant to define compounds which have been chosen based on the configuration of the interacting domains of the present invention. As will be understood by the person of ordinary skill, macromolecules having non-naturally occurring modifications are also within the scope of the term "molecule". For example, peptidomimetics, well known in the pharmaceutical industry and generally referred to as peptide analogs can be generated by modelling as mentioned above. Similarly, in a preferred embodiment, the polypeptides of the present invention are modified to enhance their stability. It should be understood that in most cases this modification should not alter the biological activity of the protein. The molecules identified in accordance with the teachings of the present invention have a therapeutic value in diseases or conditions in which sodium transport through the sodium channels is compromised by a mutation (or combination thereof) in one of the genes identified in accordance with the present invention. Alternatively, the molecules identified in accordance with the teachings of the present invention find utility in the development of compounds which can modulate the activity of the alpha subunit sodium channels and/or the action potential in nerve cells and muscles cells (e.g. restore the fast inactivation of the sodium channel to normal levels).

As used herein, agonists and antagonists also include potentiators of known compounds with such agonist or antagonist properties. In one embodiment, modulators of the fast inactivation of the sodium channel in accordance with the present invention can be identified and selected by contacting the indicator cell with a compound or mixture or library of molecules for a fixed period of time.

As used herein the recitation "indicator cells" refers to cells that express at least one sodium channel α subunit (SCNA) according to the present invention. As alluded to above, such indicator cells can be used in the screening assays of the present invention. In certain embodiments, the indicator cells have been engineered so as to express a chosen derivative, fragment, homolog, or mutant of the combination of genotypes of the present invention. The cells can be yeast cells or higher eukaryotic cells such as mammalian cells. In one particular embodiment, the indicator cell would be a yeast cell harboring vectors enabling the use of the two hybrid system technology, as well known in the art (Ausubel et al., 1994, *supra*) and can be used to test a compound or a library thereof. In another embodiment, the *cis-trans* assay as described in USP 4,981,784, can be adapted and used in accordance with the present invention. Such an indicator cell could be used to rapidly screen at high-throughput a vast array of test molecules. In a particular embodiment, the reporter gene is luciferase or beta-Gal.

It shall be understood that the "*in vivo*" experimental model can also be used to carry out an "*in vitro*" assay. For example, cellular extracts from the indicator cells can be prepared and used in an "*in vitro*" test. A non-limiting example thereof include binding assays.

In some embodiments, it might be beneficial to express a fusion protein. The design of constructs therefor and the expression and production of fusion proteins and are well known in the art (Sambrook et al., 1989, *supra*; and Ausubel et al., 1994, *supra*).

Non-limiting examples of such fusion proteins include hemaglutinin fusions and Gluthione-S-transferase (GST) fusions and Maltose binding protein (MBP) fusions. In certain embodiments, it might be beneficial to introduce a protease cleavage site between the two polypeptide sequences which have been fused. Such protease cleavage

sites between two heterologously fused polypeptides are well known in the art.

In certain embodiments, it might also be beneficial to fuse the protein of the present invention to signal peptide sequences enabling a secretion of the fusion protein from the host cell. Signal peptides from diverse organisms are well known in the art. Bacterial OmpA and yeast Suc2 are two non-limiting examples of proteins containing signal sequences. In certain embodiments, it might also be beneficial to introduce a linker (commonly known) between the interaction domain and the heterologous polypeptide portion. Such fusion protein find utility in the assays of the present invention as well as for purification purposes, detection purposes and the like.

For certainty, the sequences and polypeptides useful to practice the invention include without being limited thereto mutants, homologs, subtypes, alleles and the like. It shall be understood that generally, the sequences of the present invention should encode a functional (albeit defective) alpha subunit of sodium channels (SCNA). It will be clear to the person of ordinary skill that whether the SCNA sequence of the present invention, variant, derivative, or fragment thereof retains its function, can be determined by using the teachings and assays of the present invention and the general teachings of the art.

It should be understood that the SCNA protein of the present invention can be modified, for example by *in vitro* mutagenesis, to dissect the structure-function relationship thereof and permit a better design and identification of modulating compounds. However, some derivative or analogs having lost their biological function may still find utility, for example for raising antibodies. These antibodies could be used for detection or purification purposes. In addition, these antibodies could

also act as competitive or non-competitive inhibitor and be found to be modulators of the activity of the SCNA proteins of the present invention.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) when such DNA has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting DNA may be maintained on a episomal element such as a plasmid. With respect to eukaryotic cells, a stably transfected cell is one in which the transfecting DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA. Transfection methods are well known in the art (Sambrook et al., 1989, *supra*; Ausubel et al., 1994 *supra*). The use of a mammalian cell as indicator can provide the advantage of furnishing an intermediate factor, which permits for example the interaction of two polypeptides which are tested, that might not be present in lower eukaryotes or prokaryotes. It will be understood that extracts from mammalian cells for example could be used in certain embodiments, to compensate for the lack of certain factors.

In general, techniques for preparing antibodies (including monoclonal antibodies and hybridomas) and for detecting antigens using antibodies are well known in the art (Campbell, 1984, In "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", Elsevier Science Publisher, Amsterdam, The Netherlands) and in Harlow et al., 1988 (in: Antibody-A Laboratory Manual, CSH Laboratories). The present invention also provides polyclonal, monoclonal antibodies, or humanized versions

thereof, chimeric antibodies and the like which inhibit or neutralize their respective interaction domains and/or are specific thereto.

From the specification and appended claims, the term therapeutic agent should be taken in a broad sense so as to also include a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to the present invention could be introduced into individuals in a number of ways. For example, cells can be isolated from the afflicted individual, transformed with a DNA construct according to the invention and reintroduced to the afflicted individual in a number of ways. Alternatively, the DNA construct can be administered directly to the afflicted individual. The DNA construct can also be delivered through a vehicle such as a liposome, which can be designed to be targeted to a specific cell type, and engineered to be administered through different routes.

For administration to humans, the prescribing medical professional will ultimately determine the appropriate form and dosage for a given patient, and this can be expected to vary according to the chosen therapeutic regimen (i.e. DNA construct, protein, cells), the response and condition of the patient as well as the severity of the disease.

Composition within the scope of the present invention should contain the active agent (i.e. molecule, hormone) in an amount effective to achieve the desired therapeutic effect while avoiding adverse side effects. Typically, the nucleic acids in accordance with the present invention can be administered to mammals (i.e. humans) in doses ranging from 0.005 to 1 mg per kg of body weight per day of the mammal which is treated. Pharmaceutically acceptable preparations and salts of the active agent are within the scope of the present invention and are well known in the art (Remington's Pharmaceutical Science, 16th Ed., Mack Ed.). For the administration of polypeptides, antagonists, agonists and the like, the

amount administered should be chosen so as to avoid adverse side effects. The dosage will be adapted by the clinician in accordance with conventional factors such as the extent of the disease and different parameters from the patient. Typically, 0.001 to 50 mg/kg/day will be administered to the mammal.

The present invention also relates to a kit for diagnosing and/or prognosing epilepsy, and/or predicting response to a medication comprising an assessment of a genotype at SCNA loci of the present invention (or loci in linkage disequilibrium therewith) using a nucleic acid fragment, a protein or a ligand, a restriction enzyme or the like, in accordance with the present invention. For example, a compartmentalized kit in accordance with the present invention includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include in one particular embodiment a container which will accept the test sample (DNA protein or cells), a container which contains the primers used in the assay, containers which contain enzymes, containers which contain wash reagents, and containers which contain the reagents used to detect the extension products.

BRIEF DESCRIPTION OF THE DRAWINGS

Having thus generally described the invention, reference will now be made to the accompanying drawings, showing by way of illustration a preferred mbodiment thereof, and in which:

Figure 1 shows the IGE candidate region on ch 2q23-q31. Order and distance between markers are according to Gyapay et al., 1994.

Figure 2 shows the PCR primers used for genomic PCR-SSCP of SCN1A;

Figure 3 shows the sequence of the SCN1A mutations found in epilepsy patients;

Figure 4 shows the PCR primers used for genomic PCR-SSCP of SCN2A;

Figure 5 shows the mutation found in epilepsy patients in SCN2A;

Figure 6 shows the PCR primers used for genomic PCR-SSCP of SCN3A; and

Figure 7 shows the mutation found in epilepsy patients in SCN3A.

Sequences are also shown in the Sequence Listing. For example, SEQ ID NO.:1 shows the nucleic acid sequence of the adult form of SCN1A; SEQ ID NO.:2 shows the nucleic acid sequence of the neonatal form of SCN1A; SEQ ID NO.:3 shows the protein sequence of the adult form of SCN1A; SEQ ID NO.:4 shows the protein sequence of the neonatal form of SCN1A; SEQ ID NOS.:5-32 show the genomic sequence of SCN1A; SEQ ID NO.:33 shows the cDNA sequence of the adult form of SCN2A; SEQ ID NO.:34 shows the cDNA sequence of the neonatal form of SCN2A; SEQ ID NO.:35 shows the protein sequence of the adult form of SCN2A; SEQ ID NO.:36 shows the protein sequence of the neonatal form of SCN2A; SEQ ID NOS.:37-64 show the genomic sequence of SCN2A; SEQ ID NO.:65 shows the cDNA sequence of the adult form of SCN3A; SEQ ID NO.:66 shows the cDNA sequence of the neonatal form of SCN3A; SEQ ID NO.:67 shows the protein sequence of

the adult form of SCN3A; SEQ ID NO.:68 shows the protein sequence of the neonatal form of SCN3A; and SEQ ID NOS.:69-98 show the genomic sequence of SCN3A. Rat SCNA1 sequences can be found in GenBank under accession numbers M22253 and X03638.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawing which is exemplary and should not be interpreted as limiting the scope of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Epilepsy is one of the most common neurological conditions, affecting 1-2% of the general population. Familial aggregation studies have shown an increased risk for epilepsy in relatives of probands with different types of epilepsy, and especially for the idiopathic generalized epilepsies (IGEs). The epilepsy genes identified to date account for a very small proportion of all the epilepsies. In addition, they have been identified in rare syndromes where the pattern of inheritance was clearly Mendelian. This is not the case for the vast majority of epileptic patients, however, where the pattern of inheritance is not compatible with a simple Mendelian model. In fact, most authors consider epilepsy to be the result of a combination of many different genetic and environmental factors, features of a complex trait. While the pattern of inheritance is not mendelian, sporadic IGE cases may be caused by specific mutations in the same genes. Based on this assumption, a large cohort of IGE patients was tested for mutation in the SCNA genes.

In order to localize the gene causing epilepsy in a large family segregating an autosomal dominant form of IGE, 41 family members, including 21 affected individuals, were genotyped. A detailed clinical description of this family has been reported elsewhere (Scheffer

and Berkovic 1997). The majority of patients in this family present a benign epilepsy syndrome occurring in childhood and characterized by frequent generalized tonic-clonic seizures not always associated with fever: a syndrome called febrile seizures plus (FS+). However, several patients presented other types of generalized seizures (GTCS) as well, such as myoclonic seizures and absences (Scheffer and Berkovic 1997). Mean age at onset was 2.2 years and offset was 11.7 years. Neurological examination and intellect were normal in all individuals except one, who had moderate intellectual disability. EEG recordings were normal in most patients. However, in three individuals generalized epileptiform activity was found and four patients had mild or moderate diffuse background slowing. Table 1 shows the different types of seizures found in the 21 patients included in this study.

Table 1. Different types of generalized seizures found in the 21 patients included in the linkage analysis.

Type of seizures	n
Febrile convulsions alone	9
GTCSs[a] + absence seizures	4
GTCSs + myoclonic seizures	1
GTCSs + atonic seizures	1
Solitary afebril GTCS	1
Secondary epilepsy + mental retardation	1
Unwitnessed events	4

[a] GTCS: generalized tonic clonic seizure

A genome wide search examining 190 markers identified linkage of IGE to chromosome (ch) 2 based on an initial positive lod score for marker D2S294 (Z=4.4, (=0). A total of 24 markers were tested on ch 2q in order to define the smallest IGE candidate region. Table 2 shows the two-point lod scores for 17 markers spanning the IGE candidate region. The highest lod score (Zmax=5.29; (=0) was obtained with marker D2S324. Critical recombination events mapped the IGE gene to a 29cM region flanked by markers D2S156 and D2S311, assigning the IGE locus to ch 2q23-q31 (Figure 1). Although the relationship of FS+ with other IGE phenotypes remains unclear, the observation that in this family, several affected individuals have different types of generalized seizures, suggests that seizure predisposition determined by the ch 2q-IGE gene could be modified by other genes and/or environmental factors, to produce different seizure types.

Table 2. Two-point lod-scores for 17 markers localized on ch 2q23-q31.

	Recombination fractions								
Locus	**0**	**0.05**	**0.1**	**0.15**	**0.2**	**0.3**	**0.4**	**Zmax**	**max**
D2S142	0.99	1.94	1.97	1.85	1.68	1.22	0.66	1.98	0.078
D2S284	1.3	1.18	1.06	0.94	0.82	0.57	0.3	1.3	0
D2S306	1.9	2.82	2.74	2.52	2.25	1.6	0.85	2.82	0.057
D2S156	2.15	3.05	2.96	2.73	2.43	1.73	0.93	3.05	0.056
D2S354	4.72	4.26	3.82	3.4	2.97	2.1	1.13	4.72	0
D2S111	5.15	4.71	4.26	3.78	3.29	2.26	1.17	5.15	0
D2S124	3.5	3.2	2.89	2.58	2.26	1.58	0.84	3.5	0
D2S382	4.31	3.93	3.54	3.14	2.74	1.91	1.02	4.31	0
D2S399	0.48	0.4	0.33	0.27	0.22	0.14	0.08	0.48	0
D2S294	4.4	4.04	3.65	3.25	2.84	2	1.07	4.4	0
D2S335	4.76	4.32	3.91	3.51	3.1	2.22	1.21	4.76	0
D2S333	1.42	1.23	1.04	0.87	0.72	0.45	0.22	1.4	0
D2S324	5.29	4.72	4.16	3.63	3.13	2.15	1.14	5.29	0
D2S384	3.85	3.52	3.17	2.82	2.45	1.69	0.89	3.85	0
D2S152	1.9	1.7	1.52	1.36	1.2	0.87	0.48	1.9	0
D2S311	-0.81	1.62	1.66	1.58	1.46	1.11	0.63	1.66	0.085
D2S155	-5.21	0.57	1.12	1.29	1.29	1.04	0.59	1.3	0.17

Haplotypes using 17 markers spanning the IGE candidate region were constructed (data not shown). The centromeric boundary was defined by a recombination event between the markers D2S156 and D2S354; whereas a recombination between the markers D2S152 and D2S311 set the telomeric boundary. These critical recombination events localized the IGE gene to a 29cM region flanked by markers D2S156 and D2S311 (Figure 1).

Over the last four decades, family studies provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures: 1) familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy. In two studies standardized morbidity ratios for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy varied from 2.5 to 3.4 in siblings and 6.7 in offspring (Anneger et al. 1982; Ottman et al. 1989); and 2) the presence of higher concordance rates for epilepsy in monozygotic than in dizygotic twins. Different studies showed concordance rates varying from 54 to 11 % in monozygotic twins and 10 to 5% in dizygotic pairs (Inouye 1960; Lennox, 1960; Harvald and Hauge 1965; Corey et al. 1991; Silanpaa et al 1991).

It is now generally accepted that seizure susceptibility probably reflects complex interactions of multiple factors affecting neuronal excitability and that most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene (Andermann 1982; Ottman et al. 1995). This of course significantly makes more complex one's ability to isolate genes which predispose or induce epilepsy. However, some specific epileptic syndromes, which aggregate in families, may result from definable monogenic abnormalities. These families present a uniqu opportunity to

rapidly map genes that play a role in determining predisposition to seizures.

To date, there are a total of six loci (Greenberg et al. 1988; Leppert et al 1989; Lewis et al. 1993; Elmslie et al. 1997; Guipponi et al. 1997; Wallace et al. 1998), for which three genes have been identified in specific IGE syndromes (Bievert et al. 1998; Singh et al. 1998; Wallace et al. 1998). Interestingly, all three genes are ion channels, including a mutation found in the Na+-channel (1 in a Tasmania family with febrile seizures and generalized epilepsy (Wallace et al. 1998). While the candidate interval identified in our kindred remains large, a number of interesting genes map to the region. These include a cluster of Na+ channel genes and K+ channel genes (electronic data base search), as well as the GAD1 gene, which encodes for glutamate decarboxylase, an enzyme involved in the syntheses of γ-aminobutyric acid (GABA) (Bu and Tobin 1994). GABA is one of the major neurotransmitters involved in synaptic inhibition in the central nervous system (Barnard et al. 1987). However, the large size of the candidate interval will require further refinement of the locus prior to the identification of the gene responsible for IGE in the kindred studied herein.

Fifty-three % (9/17) of affected individuals in the large IGE family described herein, who had their seizures classified, had only febrile convulsions. However, 41 % of patients (7/17) presented with different types of generalized seizures. These findings may indicate that, although the predisposition to IGE in this family is determined by a single gene localized on ch2q23-q31, the different types of generalized seizures occurring in the same family may have resulted from interactions among genetic and/or environmental modifiers.

In conclusion, a locus for IGE was mapped on ch 2q23-q31. This locus seems to be associated with a specific IGE syndrome, FS

+. However, the relationship of FS+ with other IGE phenotypes, and the role of the ch 2q locus in other FS+ families and in other forms of IGE are still undetermined.

Having identified a locus for IGE on chromosome 2q23-q31, it was next verified whether mutations and/or polymorphisms could be linked to epilepsy. Public data bases were screened to identify potential genes in that chromosome region. The blasts of the data bases were also oriented to identify more specifically, membrane channels since seizures in mice and human are known to be associated with membrane channels. Having identified membrane channel coding sequences or parts thereof by the computer searches, the candidate genes, potentially involved in epilepsy, had to be validated as susceptibility genes for the disease. Two approaches were used. The first one was to test the candidate genes for mutations in a family comprising members having the disease (data not shown). The second approach was as follows. Since it is known that epilepsy results from a lower seizure threshold, and that generalized epilepsy results, in many instances, from a generalized lowering of the seizure threshold, the following hypothesis was formulated. The gene which results in epilepsy in the large family (that enabled the focusing chromosome 2q23-q31) should have other, less severe, mutations that would cause epilepsy in people who have only a weak family history of epilepsy. The sodium channel genes were chosen because they are involved in key electrical functions and could thus be good candidates. To formally test the hypothesis, many (60 to 70) unrelated cases of epilepsy were tested for mutations in these candidate genes. Surprisingly, mutations were found in all three candidate genes.

In order to assess whether mutations/polymorphisms could be identified and correlated to epilepsy, a panel of 70 to 80 epileptic patients (IGE) were tested for mutations in SCN1A, SCN2A and SCN3A,

using Single-strand conformation polymorphism (SSCP). SSCP analysis enables the detection of mutations as small as single-base substitutions. Indeed, such substitutions, by altering the conformations of single-strand DNA molecules, affect the electrophoretic mobilities thereof in non-denaturing gels. Thus, one can distinguish among sequences by comparing the mobilities of wild type (wt), mutant DNA, or different alleles of a given locus. The identification of single base substitutions of genes using SSCP is well known in the art, and numerous protocols are available therefor. A non-limiting example thereof includes fluorescence-based SSCP analysis, following PCR carried out using fluorescent-labeled primers specific for the DNA regions one wishes to amplify.

Upon the identification of differences between normal and epileptic mobilities for one of the SCNA loci of the present invention, the amplified fragments were sequenced and the nucleic acid sequences between a normal patient and an epileptic patient (IGE) compared. This comparison enabled the identification of mutations in SCN1A, SCN2A, and SCN3A. To assess, whether this difference in sequence or mutation was significantly associated with the disease, SSCP analysis was performed once again using a large cohort of normal patients. This analysis enabled to show that the mutations identified by SSCP and confirmed by sequence analysis were not present in the large cohort of normal patients tested, thereby showing that the mutaions identified correlated with IGE, for the population tested.

Taken together, these results show that SCN1A, SCN2A and SCN3A are validated genes associated with epilepsy and more specifically with IGE.

This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this

discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. This invention also claims those compounds, the use of these compounds in treating epilepsy and related neurological disorders, and any use of any compounds identified using such a screening assay in treating epilepsy and related neurological disorders.

Generally, high throughput screens for one or more SCN1A, SCN2A or SCN3A (herein collectively called SCNA) sodium channels modulators i.e. candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) may be based on assays which measure biological activity of SCNA. The invention therefore provides a method (also referred to herein as a "screening assay") for identifying modulators, which have a stimulatory or inhibitory effect on, for example, SCNA biological activity or expression, or which bind to or interact with SCNA proteins, or which have a stimulatory or inhibitory effect on, for example, the expression or activity of SCNA interacting proteins (targets) or substrates.

Examples of methods available for cell-based assays and instrumentation for screening ion-channel targets are described in the review by Gonzalez et al. (Drug Discov. Today 4:431-439, 1999), and high-throughput screens for ion-channel drugs are described in review by Denyer et al. (Drug Discov. Today 3:323-332, 1998). Such assays include efflux of sodium or related ions that can be measured in a cell line (recombinant or non-recombinant) using fluorescence-based assays using

both sodium indicator dyes and voltage sensing dyes. Preferred assays employ ^{14}C guanidine flux and/or sodium indicator dyes such as SBFI and voltage sensing dyes such as DiBAC. Oxonal dyes such as $DiBAC_4$ are responsive to membrane depolarization. Hyper-polarization results in removal of the dye from the cell by passive diffusion, while depolarization results in concentration of the dye within the cell.

In one embodiment, the invention provides assays for screening candidate or test compounds which interact with substrates of a SCNA protein or biologically active portion thereof.

In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a SCNA protein or polypeptide or biologically active portion thereof.

In one embodiment, an assay is a cell-based assay in which a cell which expresses a SCNA protein or biologically active portion thereof, either natural or recombinant in origin, is contacted with a test compound and the ability of the test compound to modulate SCNA biological activity, e.g., modulation of sodium efflux activity, or binding to a sodium channel or a portion thereof, or any other measurable biological activity of SCNA is determined. Determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the release of a neurotransmitter or other compound, from a cell which expresses SCNA such as a neuronal cell, e.g. a substantia nigra neuronal cell, or a cardiac cell upon exposure of the test compound to the cell. Furthermore, determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the change in current or the change in release of a neurotransmitter from a cell which expresses SCNA upon exposure to a test compound. Currents in cells can be measured using the patch-clamp technique as

described in the Examples below using the techniques described in, for example, Hamill et al. 1981 Pfluegers Arch. 391:85-100. Alternatively, changes in current can be measured by dye based fluorescence assays described below.

Determining the ability of the test compound to modulate binding of SCNA to a substrate can be accomplished, for example, by coupling the SCNA agent or substrate with a radioisotope or enzymatic label such that binding of the SCNA substrate to SCNA can be determined by detecting the labeled SCNA substrate in a complex. For example, compounds (e.g., SCNA agents or substrates) can be labeled with $^{125}1$, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase or alkaline phosphatase. In these assays, compounds which inhibit or increase substrate binding to SCNA are useful for the therapeutic objectives of the invention.

It is also within the scope of this invention to determine the ability of a compound (e.g. SCNA substrate) to interact with SCNA without the labeling of any of the interactants. For example. a microphysiometer can be used to detect the interaction of a compound with SCNA without the labeling of either the compound or the SCNA (McConnell H.M.et al. (1992), Science 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and SCNA.

Modulators of SCNA can also be identified through the changes they induce in membrane potential. A suitable instrument for

measuring such changes is the VIPR™ (voltage ion probe reader) from Aurora Biosciences. This instrument works together with a series of voltage-sensing ion probe assays. The probes sense changes in transmembrane electrical potential through a voltage-sensitive FRET mechanism for which the ratio donor fluorescence emission to acceptor fluorescence emission reveals the extent of cell depolarization for both sodium and potassium channels. Depolarization results from transport of a quencher across the membrane and far enough away from a membrane-boundfluorescence emitter to relieve the initial quenching and produce light at the emission wavelength of the emitter. The system follows fluorescence at two wavelengths, both the intensities and ratios change during cell depolarization. The reader permits detection of sub-second, real-time optical signals from living cells in a microplate format. The system is amenable to manual operation for assay development or automation via robots for high-throughput screening.

In another embodiment, the assay is a cell-based assay comprising a contacting of a cell containing a target molecule (e.g. another molecule, substrate or protein that interacts with or binds to SCNA) with a test compound and determining the ability of the test compound to indirectly modulate (e.g. stimulate or inhibit) the biological activity of SCNAby binding or interacting with the target molecule. Determining the ability of the test compound to indirectly modulate the activity of SCNA can be accomplished, for example, by determining the ability of the test compound to bind to or interact with the target molecule and thereby to indirectly modulate SCNA , to modulate sodium efflux, or to modulate other biological activities of SCNA. Determining the ability of the SCNA protein or a biologically active fragment thereof, to bind to or interact with the target molecule can be accomplished by one of the methods described above or known in the art for determining direct

binding. In a preferred embodiment, determining the ability of the test compound's ability to bind to or interact with the target molecule and thereby to modulate the SCNA protein can be accomplished by determining a secondary activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g. intracellular Ca2+, diacylglycerol, IP3, and the like), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target -responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, such as luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter. Alternatively, recombinant cell lines may employ recombinant reporter proteins which respond, either directly or indirectly to sodium efflux or secondary messengers all as known in the art.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a SCNA protein or biologically active portion thereof, either naturally occurring or recombinant in origin, is contacted with a test compound and the ability of the test compound to bind to, or otherwise modulate the biological activity of, the SCNA protein or biologically active portion thereof is determined. Preferred biologically active portions of the SCNA proteins to be used in assays of the present invention include fragments which participate in interactions with non-SCNA molecules, (e.g. other channels for sodium, potassium or Ca+ or fragments thereof, or fragments with high surface probability scores for protein-protein or protein-substrate interactions). Binding of the test compound to the SCNA protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the SCNA protein or biologically active portion thereof

with a known compound which binds SCNA to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a SCNA protein, wherein determining the ability of the test compound to interact with a SCNA protein comprises determining the ability of the test compound to preferentially bind to SCNA or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a SCNA protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the SCNA protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished, for example, by determining the ability of the SCNA protein to bind to a SCNA target molecule by one of the methods described above for determining direct binding. Determining the ability of the SCNA protein to bind to a SCNA target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA, Sjolander, S. and Urbaniczky, C. (1991) Anal. Chem. 63:2338-2345 and Szabo et al. (1995) Curr. Opin. Struct. Biol. 5:699- 705). As used herein, "BIA" refers to a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g. BIA core). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished by determining the ability of the test compound to modulate the activity of an upstream or downstream effector of a SCNA target

molecule. For example, the activity of the test compound on the effector molecule can be determined or the binding of the effector to SCNA can be determined as previously described.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g. a sodium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n- dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl- N -methylglucamide, Triton® X-lOO, Triton®X-114, Thesit®, Isotridecypoly(ethylene glycol ether)n. 3-[(3- cholamidopropyl)dimethy-amino]-l-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamino]-2-hydroxy-l-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammnonio-l-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either SCNA or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a. test compound to a SCNA protein or interaction of a SCNA protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes and micro-centrifuge tubes. In one embodiment a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example. glutathione-S-transferase/SCNA fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto

glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or SCNA protein and the mixture incubated under conditions conducive to complex formation (e.g. at physiological conditions for salt and pH). Following incubation the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of SCNA binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices (and well-known in the art) can also be used in the screening assays of the invention. For example, either a SCNA protein or a SCNA target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated SCNA protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with SCNA protein or target molecules but which do not interfere with binding of the SCNA protein to its target molecule can be derivatized to the wells of the plate, and unbound target or SCNA protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST -immobilized complexes, include immunodetection of complexes using antibodies reactive with the SCNA protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the SCNA protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate vesicular traffic and protein transport in a cell, e.g. a neuronal or cardiac cell using the assays described in for example Komada M. et al. (1999) Genes Dev.13(11):1475-85, and Roth M.G. et a1. (1999) Chem. Phys. Lipids. 98(12):141-52.

In another preferred embodiment candidate, or test compounds or agents are tested for their ability to inhibit or stimulate or regulate the phosphorylation state of a SCNA channel protein or portion thereof, or an upstream or downstream target protein, using for example an *in vitro* kinase assay. Briefly, a SCNA target molecule (e.g. an immunoprecipitated sodium channel from a cell line expressing such a molecule), can be incubated with radioactive ATP , e.g., [gamma-32P] - ATP , in a buffer containing MgCl2 and MnCl2, e.g., 10 mM MgCl2 and 5 mM MnCl2. Following the incubation, the immunoprecipitated SCNA target molecule (e.g. .the sodium channel), can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the auto radiograph indicates that the SCNA substrate, e.g., the sodium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the SCNA substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. et al. (1999) Biol. Chem. 380(5):569-78.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to associate with (e.g. bind) calcium, using for example, the assays described in Liu L. (1999) Cell Signal. 11(5):317-24 and Kawai T. et al. (1999) Oncogene 18(23):3471-80.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate chromatin formation in a cell using for example the assays described in Okuwaki M. et al. (1998) J. Biol. Chem. 273(51):34511-8 and Miyaji- Yamaguchi M. (1999) J. Mol. Biol. 290(2): 547-557.

In yet another preferred embodiment candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. et al. (1995) Cell Prolif. 28(1):1-15, Cheviron N. et al. (1996) Cell Prolif. 29(8):437-46. Hu Z. W. et al. (1999) J: Pharmacol. Exp. Ther. 290(1):28-37 and Elliott K. et al. (1999) Oncogene 18(24):3564-73.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to regulate it's association with the cellular cytoskeleton. Using for example, the assays similar to those described in Gonzalez C. et al. (1998) Cell Mol. Biol. 44(7):1117-27 and Chia C.P. et al. (1998) Exp. Cell Res. 244(1):340-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. et al. (1985) J. Biol. Chem. 260(8):4740-4 and Barker J.L. et al. (1984) Neurosci. Lett. 47(3):313-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cytokine signaling in a cell, (e.g., a neuronal or cardiac cell), the assays described in Nakashima Y. et al. (1999)J: Bone Joint Surg. Am. 81 (5):603-15.

In another embodiment, modulators of SCNA expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of SCNA mRNA or protein in the cell is determined. The level of expression of SCNA mRNA or protein in the presence of the candidate compound is compared to the level of expression of SCNA mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of SCNA expression based on this comparison. For example, when expression of SCNA mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of SCNA mRNA or protein expression. Alternatively, when expression of SCNA mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of SCNA mRNA or protein expression. The level of SCNA mRNA or protein expression in the cells can be determined by methods described herein or other methods known in the art for detecting SCNA mRNA or protein.

The assays described above may be used as initial or primary screens to detect promising lead compounds for further development. Often, lead compounds will be further assessed in additional, different screens. Therefore, this invention also includes secondary SCNA screens which may involve electrophysiological assays utilizing mammalian cell lines expressing the SCNA channels such as

patch clamp technology or two electrode voltage clamp and FRET-based voltage sensor. Standard patch clamp assays express wild type and mutant channels in *Xenopus* oocytes, and examine their properties using voltage-clamp electrophysiological recording. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds.

Tertiary screens may involve the study of the identified modulators in rat and mouse models for epilepsy. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an test compound identified as described herein (e.g., a SCNA modulating agent, an antisense SCNA nucleic acid molecule, a SCNA-specific antibody, or a SCNA-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment (e.g. treatments of different types of epilepsy or CNS disorders), as described herein.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic

library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des. 12: 145, 1997). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993) Science 261 :1303; Carrell et al. (1994) Angew. Chem, Int. Ed Engl. 33:2059; Carell et al. (1994) Angew. Chem. Jnl. Ed. Engl. 33:2061; and in Gallop et al. (1994). Med Chem. 37:1233. Libraries of compounds may be presented in solution (e.g.. Houghten (1992) Biotechniques 13:412-421). or on beads (Lam (199]) Nature 354:82-84), chips (Fodor (1993) Nature 364:555-556). bacteria (Ladner USP 5.223,409), spores (Ladner USP '409), plasmids (Cull et al.(1992) Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith (1990); Science 249:386-390). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad .Sci. USA 91: 11422; Zuckermann et al. (1994), .J: Med. Chem. 37:2678; Cho et al. (1993), Science 261 :1303; Carrel1 et al. (1994) Angew. Chem Int. Ed. Engl. 33:2059, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is recognized by the inventors that certain therapeutic agents have been identified for cardiac, muscular, chronic pain, acute pain and other disorders, and analgesics and anesthetics that are modulators of sodium channels. Use of these sodium channel modulators

for treating epilepsy and related neurological disorders also falls within the scope of this invention. In one embodiment of this invention, sodium channel blockers are modified to achieve improved transport across the blood brain barrier in order to have direct effect on neuronal SCNA proteins and genes. Descriptions of such compounds are found at Hunter, JC et al. Current Opinion in CPNS Invest. Drugs. 1999 1(1):72-81; Muir KW et al. 2000. Cerebrovasc. Disc. 10(6):431-436; Winterer, G. 2000. Pharmacopsychiatry 33(5):182-8; Clare et al. 2000. Drug. Discov. Today 5(11):506-520; Taylor CP et al. 2000. Adv. Pharmacol. 39:47-98, and Pugsley MK et al. 1998. Eur. J. Pharmacol. 342(1)93-104.

It is also recognized by the inventors that compounds which modulate (i.e. either upregulate or downregulate) transcription and translation of SCNA genes are useful for treating epilepsy or related neurological disorders. According to this invention, test compounds which modulate the activity of promoter elements and regulatory elements of sodium channel genes are useful for treating these disorders.

In summary, based on the disclosure herein, those skilled in the art can develop SCNA screening assays which are useful for identifying compounds which are useful for treating epilepsy and other disorders which relate to potentiation of SCNA expressing cells. The assays of this invention may be developed for low-throughput, high-throughput, or ultra-high throughput screening formats.

The assays of this invention employ either natural or recombinant SCNA protein. Cell fraction or cell free screening assays for modulators of SCNA biological activity can use *in situ*, purified, or purified recombinant SCNA proteins. Cell based assays can employ cells which express SCNA protein naturally, or which contain recombinant SCNA gene constructs, which constructs may optionally include inducible promoter sequences. In all cases, the biological activity of SCNA can be

directly or indirectly measured; thus modulators of SCNA biological activity can be identified. The modulators themselves may be further modified by standard combinatorial chemistry techniques to provide improved analogs of the originally identified compounds.

Finally, portions or fragments of the SCNA cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome and thus, locate gene regions associated with genetic disease (mutations/polymorphisms) related to epilepsy or CNS disorders that involve SCNA directly or indirectly; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

The present invention is illustrated in further detail by the following non-limiting examples.

EXAMPLE 1

Molecular analysis

Genomic DNA was extracted from blood samples (Sambrook et al. 1989) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. A panel of 210 dinucleotide (CA)n repeat polymorphic markers with high heterozygosity (75%) were chosen from the 1993-94 Généthon map (Gyapay et al. 1994). Dinucleotide markers were spaced an average of 20 cM from each other throughout the 22 autosomes.

Genotyping of microsatellite markers was accomplished by polymerase chain reaction (PCR). The reaction mixture was prepared in a total volume of 13µl, using 80ng genomic DNA; 1.25µl 10x buffer with 1.5mM MgCl2; 0.65µl BSA (2.0mg/ml); 100ng of ach

oligonucleotide primer; 200mM dCTP, dGTP and dTTP; 25mM dATP; 1.5mCi [35S] dATP; and 0.5units Taq DNA polymerase (Perkin-Elmer). Reaction samples were transferred to 96 well plates and were subjected to: 35 cycles of denaturation for 30 seconds at 94°C, annealing for 30 seconds at temperatures varying from 55°C to 57°C depending on the specificity of the oligonucleotide primers, and elongation for 30 seconds at 72°C. PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels.

EXAMPLE 2

Genetic analysis

Two-point linkage analysis was carried out using the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). Precise values for Zmax were calculated with the ILINK program from the same computer package. Lod scores were generated based on an autosomal dominant mode of inheritance, 80% penetrance, disease gene frequency of 1:500 and allele frequencies for all allele markers calculated from the pedigree using the computer program ILINK (Lathrop et al. 1984).

EXAMPLE 3

Mutations in SCN1A in IGE patients

Genomic DNA form IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 2. Following PCR, SSCP analysis was performed and mutations in SCN1A were identified as follows (Figure 3):
(1) Glu1238Asp; normal: GCA TTT GAA GAT ATA; patient R10191 who has an idiopathic generalized epilepsy (IGE): GCA TTT GAC GAT ATA (found in 1 of 70 IGE patients). The mutation is thus a conservative aa

change, in the extracellular domain between III-S1 and III-S2. Furthermore, this residue is located at the junction between the TM domain and the extracellular domain. It may thus influence gating activity. The aa change between adult and neonatal isoforms is at a similar juxta-TM domain position (between I-S3 and I-S4).

(2) Ser1773Tyr; normal: ATC ATA TcC TTC CTG, patient R9049 (affected with IGE): ATC ATA TmC TTC CTG :(TCC>TAC). This mutation is in the middle of IV-S6 TM domain; found in 1/70 IGE patients, and 0/150 control subjects tested. This mutation is interesting from a biological point of view for a number of reasons. First, this region of SCN gene (IV-S6) has been found to play a critical role in fast inactivation of the SCN, by mutagenesis experiments in rat SCN (McPhee et al., 1998). This is highly relevant for pathophysiology of epilepsy, since this may increase neuronal hyperexcitability. Moreover, in patients with GEFs, a mutation has been found in the SCNB1 subunit, causing impairment of the fast inactivation of the SCN (Wallace et al, 1999). Finally, many of the antiepileptic drugs (e.g. phenytoin, carbamazepine) primarly act by reducing the repetivive firing of neuron, which also involves fast inactivation of the SCN.

EXAMPLE 4

Mutations in SCN2A in IGE patients

Genomic DNA form IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 4. Following PCR, SSCP analysis was performed and mutations in SCN2A were identified as follows (Figure 5):

(1) Lys908Arg: normal: TAC AAA GAA for patient numbers always preceded by R; R9782 (Patient with IGE): TAC AGA GAA. The mutation is thus a conservative aa change, located in an extracellular domain

between TM domains IIS5 and IIS6; in 1/70 IGE patients; 0/96 normal controls. The mutation involves an important component of the SCN gene, since the S5 and S6 segments are thought to form the wall of the transmembrane pore which allows the sodium to enter the cell. This may have an influence on the gating control of the pore.

(2) Leu768Val, in individuals R8197, R9062 and R9822 (all IGE patients) (found in 3/70 IGE patients and 0/65 control subjects). The mutations is in the IV-S6 component of the sodium channel, which is important in the inactivation of the channel (see above for more detail).

EXAMPLE 5

Mutations in SCN3A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 6. Following PCR, SSCP analysis was performed and mutations in SCN3A were identified as follows (Figure 7):

(1) Asn43DEL: allele 1: CAA GAT AAT GAT GAT GAG ; allele 2: CAA GAT --- GAT GAT GAG ; in open reading frame deletes 1 aa: DNDDEN->QDDDEN, in the cytoplasmic N-terminal segment; in IGE patients, the frequency of allele 1 = 131/146 (0.90); allele 2= 15/146 (0.10); for IGE patients: homozygotes (22): R3958, R9632; heterozygotes (12): R9049, R9152, R9649, R9710, R9896, R10069, R10191, R10213, R9993, R10009, R10256 . Of note, 2 patients are homozygous for the rare allele and all patients have IGE. In controls: allele 1 = 145/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes were found.

(2) normal: tggtgtaaggtag, R10670 (IGE patient): tggtataaggtag, in conserved intron between 5N & 5A exons, significance uncertain.

(3) normal: ccccttatatctccaac, R10250 (IGE patient): ccccttatayctccaac; in conserved intron between 5N & 5A exons, significance uncertain.

(4) Val1035Ile: normal: AAA TAC GTA ATC GAT, R9269 (IGE patient): AAA TAC RTA ATC GAT ; (GTA>ATA = Val>Ile). The mutation is thus a conservative aa change which destroys a SnaBI site (this could thus be used as a polymorphism identifiable by restriction enzyme digestion). In SCN1A, this Val is a Ile, therefore probably not a causative mutation. In cytoplasmic domain bw II-S6 & III-S1 TMs; found in 1/70 IGE alleles; and 0/70 controls.

EXAMPLE 6

SCN1A is involved in idiopathic generalized epilepsy

The assumption that SCN1A gene is involved in idiopathic generalised epilepsy in humans is based on many sets of evidence. First, a mutation has been found in a large Australian family with autosomal dominant epilepsy. The phenotype is idiopathic generalised epilepsy that is associated with febrile seizures (GEFS syndrome). The gene for this family has been previously mapped to the long arm of chromosome 2. The maximum lod score is 6.83 for marker D2S111. The candidate region is very large, spanning 21cM between markers D2S156 and D2S311. However, within this interval, there is a cluster of sodium channel genes, including SCN1A which was hypothesized to be a candidate gene for the disease.

Screening by SSCP of a small panel of three (3) affected patients form the family, and 3 normal controls was carried-out at first. All the exons of the SCN1A gene have been amplified by PCR, and a SSCP variant in exon 4 was found for all of the affected individuals, and none of the controls. By sequencing an affected patient and a control, an A-T substitution at nucleotide 565 was found. This variation destroys a BamHI restriction site, this nzyme was thus used as a diagnostic test to

screen all the affected patients from the family, as well as more control cases. All affected patients from the family have A565T substitution, and none of the unaffected patients in the same kindred. An A565T substitution was not found in more than 400 control chromosomes.

The A565T substitution correspond to a non-conservative amino acid change (D188V). This amino acid is conserved in all sodium channels thus far identified, in all species. The only exception is SCN2A identified in rat by Numa et al, where the aspartic acid is replaced by asparagine. However, it is likely that this represents an error during replication of cDNA, since other investigators have cloned the same gene in rat and found that the aspartic acid is conserved at position 188. Moreover, the same group has shown that D188N has a functional effect on channel activation in oocytes (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Of note, this A565T substitution has not been found in 150 epileptic patients and in 200 control patients. Thus, this substitution has yet to be identified after 700 chromosomes assessments.

In view of proving that D188V in SCN1A, identified in the large Australian family studied, is a pathogenic mutation, the oligonucleotide mismatch mutagenesis technique was used to introduce the mutation in rat SCN1A clone. RNA was isolated from mutant and wild-type clones, and injected into oocytes in view of recording sodium currents by the patch-clamp technique. The amplitude of the currents was dramatically reduced for the mutant. Also, a small shift in the inactivation curve was observed for the mutant, as compared to the wild-type. Taken together, these preliminary results confirm a functional effect of D188V mutation on SCN1A gene. (more detail below).

The results presented herein are corroborated by studies from other investigators. For example, several other groups have also found linkage to the same locus on chromosome 2 for families with

GEFS or very similar syndromes. Mutations in SCN1A (Thr875Met mutation; Arg1648His) have been found to be the cause of the epileptic syndrome in at least two (2) of these families (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Also, GEFS syndrome has been shown to be caused by mutation in SCN1B gene. It is demonstrated that the beta subunits interact with alpha subunits of voltage-gated sodium channels to alter kinetics of sodium currents in cells. These data suggest a common mechanism for generating abnormal neuronal discharges in the brain of patients with idiopathic generalised epilepsy.

Finally, in the process of screening patients from the large kindred with GEFS described above, a large cohort of patients with idiopathic generalised epilepsy was also screened by SSCP. Two (2) SSCP variants, that were subsequently sequenced were thereby identified. The variation observed are shown in Table 3:

Table 3

exon	DNA variation	IGE alleles	Control alleles
1Ax17	Glu1238Asp; conservative AA change in extracellular domain between III-S1 and III-S2	3/254	0/284
1Ax24.2	Ser1773Tyr; middle of IV-S6 TM domain	1/252	0/334

Previous functional studies have shown that amino acid substitution in the IV-S6 transmembrane domain of SCN2A significantly affects the rate of inactivation of the channel. It is thus likely that Ser1773Tyr will have an effect on the SCN1A gene function. Such functional studies are currently underway.

EXAMPLE 7

Further validation of the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE and epilepsy in general

A number of methods could be used to further validate the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE. For example, additional patients could be screened for mutations in SCN1A, SCN2A, or SCN3A. Furthermore, additional normal patients could be screened in order to validate that the mutations identified significantly correlate with disease, as opposed to reflecting a polymorphism which is not linked to IGE. Polymorphisms which are not directly linked to IGE, if in linkage disequilibrium with a functional mutation

linked to IGE, could still be useful in diagnosis and/or prognosis assays. In addition, functional studies can be carried. Numerous methods are amenable to the skilled artisan. One particularly preferred functional assay involves the use of Xenopus oocytes and recombinant constructs harboring normal or mutant sequence of SCN1A, SCN2A, or SCN3A. Xenopus oocytes have been used in functional assays to dissect the structure-function relationship of the cyclic AMP-modulated potassium channel using recombinant KCNQ2 and KCNQ3 (Schroeder et al., 1998). As well, it has been used to dissect the structure-function relationship of the beta subunit of the sodium channel (SCN1B gene; Wallace et al. 1998).

One such example of functional studies was investigated by assessing the effects of mutation D188V in the SCN1A gene on sodium channel function by introducing the mutation into a cDNA encoding the rat ortholog SCN1A gene. This rate gene shares > 95% identity with the human SCN1A gene. The expression of wild type and mutant channels in *Xenopus* oocytes, and the examination of their properties using voltage-clamp electrophysiological recording is amenable to this *Xenopus* system. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds. Among the channel properties that are likely to be altered by mutations linked to epilepsy are: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels; 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. Preliminary results indicate that D188V mutant channels are identical to wild type channels with respect to the voltage-dependence of activation and to inactivation time course. However, steady state inactivation for the mutant channels is shifted to membrane potentials that are slightly more positive than observed in wild type channels. This positive shift should increase the fraction of channels available to open at rest. This could increase neuronal excitability and contribute to epileptogenesis. Thus, a functional consequence of a naturally occurring mutation in a sodium channel gene has been tentatively identified. Thus, the functional consequence of the D188M mutant could at least in part explain its role in epilepsy. Such a functional consequence is expected to be observed with other mutations identified above in SCNA1, SCNA2 and SCNA3.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

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WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to epilepsy and/or development of epilepsy, as well as predicting this individual's response to medication, said method comprising the step of determining the genotype of at least one gene selected from SCN1A, SCN2A and SCN3A of the individual, or of a DNA variant, equivalent, or mutation which shows a linkage disequilibrium therewith, thereby determining an individual's predisposition to epilepsy and/or development of epilepsy.

2. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises restriction endonuclease digestion.

3. The method of claim 1 or 2, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises hybridizing with allele specific oligonucleotides.

4. The method of claim 1, which further comprises a step, prior to determining the SCN1A, SCN2A or SCN3A genotype, of amplifying a segment of the the SCN1A, SCN2A or SCN3A using polymerase chain reaction.

5. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises a sequencing of SCN1A, SCN2A or SCN3A , or parts thereof.

6. The method of claim 1, wherein the SCN1A, SCN2A or SCN3A genotype is determined using a polymorphic variant

site in linkage disequilibrium with at least one allelic variant or mutant identified in accordance with the present invention.

7. An assay for screening a test agent and selecting an agent which modulates inactivation of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying a function of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the inactivation of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

8. An assay for screening a test agent and selecting an agent which modulates the activity of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying the activity of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the activity of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

9. A method of using specific alleles of the SCN1A, SCN2A or SCN3A genes, or a variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith, to set-up a screening assay

for agents destined to modulate sodium channel function for the purpose of identifying agents having an application in epilepsy therapy.

10. A method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising:

a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;

b) contacting said screening assay with a test compound; and

c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

11. The method of claim 10, wherein the test compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide further analogs of said test compound also having said therapeutic effect.

12. A compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising,

a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;

b) contacting said screening assay with a test compound; and

c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

13. The compound of claim 12, wherein the compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide analogs of said compound also having said therapeutic effect.

Ch 2q23-q31

Centromere

1cM — **D2S142**

D2S284

4cM

4cM — **D2S156/ D2S354**

D2S111

5cM

D2S294

2cM

D2S335

IGE locus

6cM

29 cM

2cM — **D2S324**

2cM — **D2S384**

D2S152

8cM

Telomere

D2S311

Fig. 1

1Ax00.1
NaC-340 TGTGTTCTGCCCCAGTGAGACT,
NaC-341 CTTCCTGCTCTGCCCAAACTGAAT
257 bp 53.4C

1Ax00.2
NaC-342 GGCGATGTAATGTAAGGTGCTGTC,
NaC-343 GTGCCTTCAGTTGCAATTGTTCAG
259 bp 54.5C

1Ax01.1
NaC-268, TTAGGAATTTCATATGCAGAATAA,
NaC-269 TGGGCCATTTTTCGTCGTC
201 bp 50.9C

1Ax01.2
NaC-270 GAAAGACGCATTGCAGAAGAAAAGG,
NaC-271 CTATTGGCATGTGTTGGTGCTACA
277 bp 54.4C

1Ax02
NaC-45 GTGCTGGTTTCTCATTTAACTTTAC,
NaC-46 TTCCCAACTTAATTTGATATTTAGC
319 bp 49.9C

1Ax03
NaC-87, GCAGTTTGGGCTTTTCAATGTTAG,
NaC-88, GACACAGTTTCARAATCCCRAATG
234 bp 48.9C

1Ax04
NaC-63, TTAGGGCTACGTTTCATTTGTATG,
NaC-64, AGCACTGATGGAAAACCAAACTAT
338 bp 50.8C

1Ax05
NaC-164 AGCCCATGCAGTAATATAAATCCT,
NaC-165 TCCAGGCTGATAAGCTATGTCTAA
488 bp 52.8C

FIG - 2

1Ax06
NaC-276, CTGTGGCCTGCCTGAGCGTATT,
NaC-277 CCAATTCTACTTTTTAAGGAAATG
248 bp 50.3C

1Ax07
NaC-272, AAATACTTGTGCCTTTGAA,
NaC-273, GTACATACAATATACACAGATGC
240 bp 46.7C

1Ax08
Nac-89, AGGCAGCAGAACGACTTGTAATA,
NaC-90, ATCCGGTTTTAATTTCATAACTCA
267 bp 51.9C

1Ax09.2
NaC-217 GTTGAGCACCCTTAGTGAATAATA,
NaC-218 TCACACGCTCTAGACTACTTCTCT
337 bp 52.7C

1Ax10a NaC-29, TGCAAATACTTCAGCCCTTTCAAA,
NaC-30, TTCCCCACCAGACTGCTCTTTC
239 bp 55.1C

1Ax10a
NaC-31, GCAGCAGGCAGGCTCTCA,
NaC-32, TCTCCCATGTTTTAATTTTCAACC
293 bp 54.5C

1Ax10b
NaC-67, ATAATCTTGCAAAATGAAATCACA,
NaC-68, ATCCGGGATGACCTACTGG
307 bp 53.7C

1Ax10b
NaC-65, GATAACGAGAGCCGTAGAGATTCC,
NaC-66, AGCCAGCCATGCCTGAACTA
282 bp 56.4C

Fig 2 (cont'd)

1Ax10c
NaC-39, TGTTTGCTTGTCATATTGCTCAA,
NaC-40, TGCACTATTCCCAACTCACAAA
286 bp 50.7C

1Ax11.1
NaC-69 AAGGGTGTCTCTGTAACAAAAATG,
NaC-70, GTGATGGCCAGGTCAACAAA
269 bp 50.8C

1Ax11.2
NaC-71 CTGGGACTGTTCTCCATATTGGTT,
NaC-72, TTTGCAGGGGCCAGGAAG
294 bp 53.3°C

1Ax12
NaC-41 CATTGTGGGAAAATAGCATAAGC,
NaC-42, GCAAGAACCCTGAATGTTAGAAA
334 bp 51.2C

1Ax13.1
NaC-92 TAATGCTTTTAAGAATCATACAAA,
NaC-93, CCAGCGTGGGAGTTGACAATC
256 bp 51.1C

1Ax13.2
NaC-75 CGGCATGCAGCTCTTTGGTA,
NaC-91, ATGTGCCATGCTGGTGTATTTC
277 bp 55.6C

1Ax14.1
NaC-79 CACCCATCTTCTAATCACTATGC,
NaC-80, CAGCAATTTGGAGATTATTCATT
254 bp 50.4C

1Ax14.2
NaC-81 GCAGCCACTGATGATGATAA,
NaC-82, CTGCCAGTTCCTATACCACTT
269 bp 49.4C

Figure 2 (cont'd)

1Ax14.3
NaC-83 TACAGCAGAAATTGGGAAAGAT,
NaC-84, GTATTCATACCTACCCACACCTAT
269 bp 50.2C

1Ax15
NaC-202 TTCTTGGCAGGCAACTTATTACC,
NaC-203 TAAGCTGCACTCCAAATGAAAGAT
233 bp 53.1C

1Ax16.1
NaC-187, GGCTGAATGTTTCCACAACT,
NaC-168 GTTCAACTATTCGGAAACACG
277 bp 51.4C

1Ax16.2
NaC-188, AGGCAGAGGAAAACAATGG,
NaC-189, ACAAGGTGGGATAATTAAAAATG
234 bp 50.3C

1Ax17
NaC-143, GTTTCTCTGCCCTCCTATTCC,
NaC-144, AAGCTACCTTGAACAGAGACA
330 bp 48.8C

1Ax18
NaC-139, AATGATGATTCTGTTTATTA,
NaC-140, AATTTGCCATTCCTTTTG
272 bp 46.1C

1Ax19.1
NaC-219 TTGACATCGAAGACGTGAATAATC,
NaC-220 CCATCTGGGCTCATAAACTTGTA
285 bp 49.3C

1Ax20
NaC-338 CCCTTTGAAAATTATATCAGTAA,
NaC-339 ATTTGGTCGTTTATGCTTTATTC
230 bp 47.6C

Fig. 2 (cont'd)

1Ax21
NaC-252, TCCAGCACTAAAATGTATGGTAAT,
NaC-253, ATTTGGCAGAGAAAACACTCC
261 bp 49.8C

1Ax22
NaC-254, TTTTAGCCATCCATTTTCTATTTT,
NaC-255, TATTTTCCCCCATATCATTTGA
223 bp 49.1C

1Ax23.1
NaC-256 TTTGCAAGAAACTAGAAAGTC,
NaC-257 TTGATGCGTGACAAAATGG
250 bp 48.3C

1Ax23.2
NaC-258 GACCAGAGTGAATATGTGACTACC,
NaC-259 CTGGGATGATCTTGAATCTAATC
246 bp 49.5C

1Ax24.1
NaC-221 GCAACTCAGTTCATGGAATTTGAA,
NaC-222 CTTGTTTTCGTTTTAAAGTAGTA
289 bp 56.1C

1Ax24.2
NaC-213 CAAAGATCACCCTGGAAGCTCAGTT,
NaC-223 TTCAAGCGCAGCTGCAAACTGAGAT
277 bp 55.8C

1Ax24.3
NaC-260 ACATCGGCCTCCTACTCTTCCTA,
NaC-261 ACAGATGGGTTCCCACAGTCC
268 bp 55.3C

1Ax24.4
NaC-262 TAACGCATGATTTCTTCACTGGTT,
NaC-263 ATCCCAAAGATGGCGTAGATGA
262 bp 54.9C

Fig. 2 (cont'd)

1Ax24.5
NaC-308, TGAGAAATAGGCTAAGGACCTCTA,
NaC-309 CCTAGGGGCTGGATTCC
244 bp 53.2C

1Ax24.6
NaC-310, AAGGGGTGCAAACCTGTGATTTT,
NaC-311 AGGGCCATGTGGTTGCCATAC
252 bp 53.4C

1Ax24.7
NaC-312 CTTCCGGTTTATGTTTTCATTTCT,
NaC-313 TCTTTATTAGTTTTGCACATTTTA
278 bp 48.4C

1Ax24.8
NaC-364 CAATCCTTCCAAGGTCTCCTATC,
NaC-365 TTTCATCTTTGCCTTCTTGCTCAT
326 bp 52.4C

1Ax24.9
NaC-366 CATGTCCACTGCAGCTTGTCCA,
NaC-367 TCCCCTTTACACAGAGTCACAGTT
292 bp 53.1C

Fig 2 (cont'd)

a. Glu1238Asp:

normal:	GCA TTT GAA GAT ATA;
patient R10191 with IGE:	GCA TTT GAC GAT ATA.

b. Ser1773Tyr:

normal:	ATC ATA TcC TTC CTG;
patient R9049 with IGE:	ATC ATA TmC TTC CTG; TCC>TAC

Fig 3

2Ax00.1 NaC-235 ATGGGTTGAATGACTTTCTGACAT, NaC-236, AGGCATTTCCTGTACAGGGACTAC
266 bp 52.7C

2Ax00.2 NaC-237 ACAGGAAATGCCTCTTCTTACTTC, NaC-238, TTTCCCCAAGGATTCTACTACTGT
277 bp 50.6C

2Ax01 NaC-100, AGTGCATGTAACTGACACAATCAC, NaC-101, CTTGCGTTCCTGTTTGGGTCTCT
241 bp 53.7C

2Ax01 NaC-11 TCCGCTTCTTTACCAGGGAATC, NaC-102, AGGCAGTGAAGGCAACTTGACTAA
259 bp 55.1C

2Ax02 NaC-96, CAGGGCAATATTTATAAATAATGG, NaC-97, TTTGGAAAATGTGTAGCTCAATAA
289 bp 48.7C

2Ax03 NaC-43, AAGGCATGGTAGTGCATAAAAG, NaC-44, ATGAAACATAAAGGGAGGTCAA
201 bp 49.3°C

2Ax04 NaC-47, AATGTGAGCTTGGCTATTGTCTCT, NaC-48, ATAGGCTCCCACCAGTGATTTAC
213 bp 50.9°C

2Ax05 NaC-49, AGGCCCCTTATATCTCCAACTG, NaC-50, CAACAAGGCTTCTGCACAAAAG
241 bp 53.9°C

2Ax05.2 NaC-110, CTTGGTGGCTTGCCTTGAC, NaC-111, TCATGAGTGTCGCCATCAGC
223 bp 51.1C

Fig 4

2Ax05.3 NaC-112, GGAAAGCTGATGGCGACACT, NaC-113, CTGAGACATTGCCCAGGTCC
329 bp 53.0C

2Ax05.4 NaC-114, TTTTTACCCGTTGCTTTCTTTA, NaC-115, TATCCCTTGCTCTTTCATTTATCT
224 bp 50.9C

2Ax06.1 NaC-169, GCCGGTAAAATAGCTGTTGAGTAG, NaC-170, GCCATTGCAAACATTTATTTCGTA
206 bp 53.3C

2Ax06.2 NaC-171, GCGTGTTTGCGCTAATAG, NaC-172, CTAAGTCACTTGATTCACATCTAA
295 bp 48.0C

2Ax07 Nac-196, ACAGGGTGGCTGAAGTGTTTTA, NaC-197, GTGGGAGGTGGCAGGTTATT
199 bp 52.6C

2Ax08 NaC-118, CAATTAGCAGACTTGCCGTTATT, NaC-119, TCTCTTGAGTTCGGTGTTTTATGA
252 bp 52.9C

2Ax09 NaC-120, ACCGAACTCAAGAGAATTGCTGTA, NaC-121, AAAGGACCGTATGCTTGTTCACTA
334 bp 52.9C

2Ax10a.1 NaC-161 TATGAATGCGCATTTTACTCTTTG, NaC-156, TGGAGCTCAACTTAGATGCTACTG
286 bp 52.1C

2Ax10a.2 NaC-13 GGTGCTGGTGGGATAGGAGTTTTT, NaC-162, TCCATTAAATTCTGGCATATTCTT
316 bp 50.9C

2Ax10b.1 NaC-145 TCAGAGGGGTGCTTTCTTCCACAT, NaC-14, CTTCGGCTGTCATTGTCCTCAAAG
298 bp 55.6C

Fig 4 (cont'd)

2Ax10b.2 NaC-146,GCAAAGGACATTGGCTCTGAGAAT, NaC-147, CTGCCTGCACCAGTCACAACTCT
324 bp 59.4C

2Ax10c NaC-190, TGGGCTTTGCTGCTTTCAA, NaC-191, AGTAACTGTGACGCAGGACTTTTA
218 bp 51.5C

2Ax11.1 NaC-148, CCCTGTTCCTCCAGCAGATTA, NaC-70, GTGATGGCCAGGTCAACAAA
283 bp 51.5C

2Ax11.2 NaC-149,TTTGATTTGGGACTGTTGTAAAC, NaC-150, AAGGCAATTATAAACTCTTTCAAG
233 bp 52.0C

2Ax12 NaC-159, TGGGAGTTAAATTAAGTTGCTCAA, NaC-160, ACATTTTATGAACACTCCCAGTTA
285 bp 50.4C

2Ax13.1 NaC-239 ATTAACACTGTTCTTGCTTTTAT, NaC-240, GTGCCAGCGTGGGAGTTC
239 bp 51.1C

2Ax13.2 NaC-241 GTGGGGGCTCTAGGAAACCT, NaC-242, TTTAATGAAAATGAGGAAAATGTT
324 bp 53.7C

2Ax14.1 NaC-134, GACCAAGCATTTTTATTTCATTC, NaC-135, AGTGGCAGCAAGATTGTCA
234 bp 49.6C

2Ax14.2 NaC-136, GGCCTTGCTTTTGAGTTCC, NaC-137, GGTCTTTGCCTATTTCTATGGTG
257 bp 51.1C

Fig 4 (cont'd)

2Ax14.3 NaC-266, TTAAACCGCTTGAAGATCTAAATA, NaC-267, TATACACCAAAATATCTCCTTAT
319 bp 48.5C

2Ax15 NaC-314 GGGGCACACCTAATTAATTTTTAT, NaC-315, AAAGAGGATACTCAAGACCACATA
(247 bp) 51.5C

2Ax16 NaC-344 CCCACCAACACAAATATACCTAAT, NaC-345, TGAAGGGAAAGGGAAAAGATTT
283 bp 52.2C

2Ax17 NaC-346 TCCAGCCTTAGGCACCTGATAA, NaC-347, ATAAAGCAGCAAAGTGCAGCATAC
310 bp 52.4C

2Ax18 NaC-348 AAGGCTGAACTGTGTAGACATTTT, NaC-349, TGACATTTCCATGGTACAAAGTGT
262 bp 52.2C

2Ax19.1 NaC-350 TTTGTTGTTGGCTTTTCACTTAT, NaC-351, CCACCTGGCAGTTTGATTG
268 bp 51.9C

2Ax19.2 NaC-352 TAAGCGTGGTCAACAACTACAGT, NaC-353, ATTCTTGCCAGCATTTATTGTC
260 bp 50.2C

2Ax20 NaC-354 CAAAACATTGCCCCAAAAG, NaC-355, TCAAACTAAACAATTTCCCTCTAA
239 bp 48.1C

2Ax21 NaC-306, GATAATTAAAAACTCACTGATGTA, NaC-307, GGAGGCTAAAGGAAAGAGTATG
288 bp 46.6C

2Ax22 NaC-356 ATTTTATAGCCAGCAAAGAACAC, NaC-357, CTAGAAATTCGGGCTGTGAA
230 bp 49.6C

Fig. 4 (cont'd)

2Ax23.1 NaC-358 CTGCTTTGTGACCTAAGGCAAGTT, NaC-359, GTGACCATGTTAAGGCAGATGAGG
290 bp 51.4C

2Ax23.2 NaC-360 GGAATGGTCTTTGATTTTGTAACC, NaC-361, TCCTTAACTGAATAAAAGCACCTC
290 bp 51.6C

2Ax24.1 NaC-207 TGGAACACCCATCAAAGAAGATACT, NaC-208, GTGGGAGTCCTGTTGACACAAAC
278 bp 52.8C

2Ax24.2 NaC-209 AGCGATTCATGGCATCAAAC, NaC-210, ACGTGGTGGAAGGCGTCATA
270 bp 52.9C

2Ax24.3 NaC-211 GCGACCCAGTTTATAGAGTTTGCC, NaC-212, CTTGTTTGCGTTTCAACGTGGTC
289 bp 56.1C

2Ax24.4 NaC-213 CAAAGATCACCCTGGAAGCTCAGTT, NaC-214, ATCCAGGGCATCTGCAAAATCAGAA
277 bp 55.8C

2Ax24.5 NaC-215 TGCCTATGTTAAGAGGGAAGTTGGG, NaC-216, ATGACCGCGATGTACATGTTCAG
279 bp 55.3C

2Ax24.6 NaC-278 TCAATTGTTTACAGCCCGTGATG, NaC-279, TTTATACAAAGGCAGACAACAT
302 bp 52.0C

2Ax24.7 NaC-280 AGGCGTAATGGCTACTCAGACGA, NaC-281, GTAATCCCTCTCCCCGAACATAAAC
251 bp 53.8C

2Ax24.8 NaC-282 TTTGATTCACGGGTTGTTTACTCTTA, NaC-283, TTCTATGGAACATTTACAGGCACATT
294 bp 52.1C

Fig 4 (cont'd)

2Ax24.9 NaC-284 TAATGTGCCTGTAAATGTTCCATAGA, NaC-285, CAGGCTTCTTAGAAAGGACTGATAGG
264 bp 50.6C

2Ax24.10 NaC-286 GTCCCAGCAGCATGACTATC, NaC-287, CCCACTGGGTAAAATTACTAAC
249 bp 49.4C

2Ax24.11 NaC-288 TAGCCATCTTCTGCTCTTGGT, NaC-289, TGGCTTCCCATATTAGACTTCTG
307 bp 51.3C

2Ax24.12 NaC-290 TCTTGCCTATGCTGCTGTATCTTA, NaC-291, AGTCGGGCTTTTCATCATTGAG
207 bp 51.8C

2Ax24.13 NaC-292 TTCTTCATGTCATTAAGCAATAGG, NaC-293, TTCAATTTAAAAGTGCTAGGAACA
299 bp 49.4C

2Ax24.14 NaC-294 CTTCAGGTGGATGTCACAGTCACTA, NaC-295, ATTCAAGCAATGCCAAGAGTATCA
263 bp 51.5C

2Ax24.15 NaC-296 CTTTCAATAGTAATGCCTTATCAT, NaC-297, TCCTGCATGCATTTCACCAAC
348 bp 49.6C

2Ax24.16 NaC-362 CTGTTCACATTTTGTAAAACTAAT, NaC-263, ATCCCAAAGATGGCGTAGATGA
309 bp 50.8C

2Ax24.17 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-363, GATCTTTGTCAGGGTCACAGTCT
269 bp 54.0C

Fig 4 (cont'd)

a. Lys908Arg:

normal: TAC AAA GAA;

9782 (Patient with IGE): TAC AGA GAA;

b. leu768val, in individuals 8197, 9062 et 9822 (all IGE patients).

FIG - 5

3Ax00a.1 NaC-390 TGTGTCCGCCAGTAGATGG, NaC-391, TTTTTGACCACAGAGGTTTACAA
233 bp 51.4C

3Ax00a.2 NaC-392 GAAGCGGAGGCATAAGCAGA, NaC-393, GGTGCAGATAATGAAATGTTTTGT
253 bp 51.3C

3Ax00b NaC-394 CACCCCTATGCCAAATGTCAAAGA, NaC-395, CAAAAACAAACTTATACCCAGAAG
293 bp 51.6C

3Ax00c NaC-396 CAAATATTGGGCAAACCCTAAT, NaC-397, AAGGTGCCATCACAAAATCAT
225 bp 50.7C

3Ax01.1 NaC-51 ATCGCTTGCTTTCCTAACTCTTGT, NaC-52, AAGTCACTATTTGGCTTTGGTTG
260 bp 53.1C

3Ax01.2 NaC-53 AGAAGCCCAAAAAGGAACAAGATA, NaC-54, GGCCCAGAAAAGTATATTACAGTT
231 bp 50.8C

3Ax02 NaC-85, TCCTTAAATAAGCCCATGTCTAAT, NaC-86, TCTCAAAGAAATTTTACAGATACT
273 bp 47.3C

3Ax03 NaC-27, AATGGCCATGGTAACCTACTAACA, NaC-28, CAGGCTATACCCACAAGGAGATT
212 bp 51.8C

3Ax04 NaC-94, TGTTAATTTTGGCTTGGATGTT, NaC-95, TCACTCCTTTGCGCTTATCAA
198 bp 50.8C

3Ax05.1 NaC-247, AGGGCTCTATGTGCCAAACC, NaC-248, AGGGGCCTACTACCTTACACCAG
213 bp 52.2C

FIG. 6

3Ax05.2 NaC-249 TGTAATCCCAGGTAAGAAGAAAC, NaC-250,
TACCGGGATGAACTGTAATAATAA
304 bp 51.8C

3Ax06.1 NaC-192,TTCTGGCACTCTTCCTCAGGTAAC, NaC-193,
GTCCCATTTGAATCCATTGTGC
261 bp 55.4C

3Ax06.2 NaC-194,GGCCCCCAAGCGATTCTG, NaC-195,
TGTACACCCACAGTCTCAACTATT
209 bp 50.3C

3Ax07 NaC-204, ACAGCCACCTTTGTAAATAA, NaC-205,
TTTTTCGCAAAGAGTTCTAT
220 bp 46.6C

3Ax08 NaC-98, AAACTGACCCTACCTCCATTTCTC, NaC-99,
ACTCAGCCTATGCTTTTCATTTCA
247 bp 53.2C

3Ax09 NaC-37 CAGATATTTATTTGGGGACATTAT, NaC-38,
AAATCTTTGCKTTTATCACTCAGT
295 bp 52.0C

3Ax10a.1 NaC-198 TAGTGCCTGGCTTTGTTTTATGAC, NaC-199,
CGGATTTGGGAAAGCTGTCTCT
225 bp 54.3C

3Ax10a.2 NaC-200 AGAGCACCTTGAAGGAAACAACAA, NaC-274,
TCCCTCAACTGAAGTACAGATAGT
253 bp 51.2C

3Ax10b NaC-33, ATAATTGCGTTCTTCCCCTACCC, NaC-34,
AAGCCCTGGCACCATCCTG
301 bp 56.2°C

3Ax10c NaC-35, _TTTGCAAAGAAATGCTATGT, NaC-36,
CTGGGTAACAGACTTCAGTAAT
303 bp 51.4°C

Fig 6 (cont'd)

3Ax11.1 NaC-122, ATGGGATTGTCTTCTCAAGTTTCT, NaC-123, GATGGCAAGATCAACAAATGGA
294 bp 50.3C

3Ax11.2 NaC-124, CTTGATCTGGGACTGCTGTGATG, NaC-125, AGGATATAATTTTTGGTTCAACA
284 bp 51.5C

3Ax12 NaC-61, TTTTCAGTGCTCTTGATAGTAGTG, NaC-62, GTGCCAATGAGCGACAGG
254 bp 50.7°C

3Ax13.1 NaC-73, CCACGTGTGGTTCTATGATACC, NaC-74, ACCGTGGGAGCGTACAGTCA
298 bp 52.3C

3Ax13.2 NaC-75, CGGCATGCAGCTCTTTGGTA, NaC-76, TGGCCACGTTCCTAGCTACTGTC
291 bp 55.9C

3Ax14.1 NaC-55, GAGTTCCCTTTTTAGGCTGTTATT, NaC-56, TCTTATTGCCTTCATGGATTTCTA
285 bp 50.5C

3Ax14.2 NaC-57, TGAAAAATAAGATGCGGGAGTG, NaC-58, GTGAGGCTGGGGTTGTTTATG
247 bp 51.7C

3Ax14.3 NaC-59, GAGATGGGAATGGAACCACCA, NaC-60, TTCGATAATGCATATAAGCACAA
297 bp 51.7C

3Ax15 NaC-318 AAGGGGGAAAATCACATCTTT, NaC-319, TTAAATGAGGCATATTCAGTCTCC
235 bp 51.8C

3Ax16 NaC-116, GGAAGTGGAGTGGGGAAGG, NaC-117, ATTCTTGCCAATATGCATTTCACT
271 bp 51.1C

Fig 6 (cont'd)

3Ax17 NaC-157,TTCTTTTGTACTCACTATTATACTAA, NaC-158, AAACTTGCCTCTTTTAAAAACAAT
317 bp 46.6C

3Ax18 NaC-374 TACCACACCCTATACCTTCAGTCA, NaC-375, GAGTATGGCACCCTTTTCTATCTA
275 bp 51.4C

3Ax19.1 NaC-386 GCTATGTTCCCCTCGCTGTCT, NaC-387, TGCTTGCCAAGAGCCTGAC
231 bp 53.6C

3Ax19.2 NaC-388 GCTGGCAAGTTCTACCACTGTG, NaC-389, CAAACGAAGAACATCAGGGAAATA
247 bp 53.0C

3Ax20 NaC-376 TTCACAATATTGTACAAAAAGTTA, NaC-377, ATTACCACCAATATTCACCATAAG
230 bp 46.4C

3Ax21 NaC-378 TCAGGGTAAGGCAAAAGTAGCAC, NaC-379, GAACCCCAGAATGAAGAAAGGTAA
294 bp 50.2C

3Ax22 NaC-380 TTTGTGAAAGTACTATTGGAACAC, NaC-381, ACGCATGGCTTTGGAACAT
204 bp 49.6C

3Ax23.1 NaC-382 CCCGTATGTGGAAGGGCTTTAT, NaC-383, CTAGGTTGATCCGGGACAAAACTA
246 bp 52.9C

3Ax23.2 NaC-384 AACGGATGACCAGGGCAAATAC, NaC-385, CTAGAAGGTCCTGGGGCAACTG
234 bp 54.8C

3Ax24.1 NaC-317 AAGCCATCATGTAAAGTGAAAAG, NaC-320, ATCCCAAAGATGGCATAGATA
274 bp 52.5C

FIG - 6 (cont'd)

3Ax24.2 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-326,
TGAGCTGCCAGGGTGAATTG
282 bp 54.9C

3Ax24.3 NaC-327 TTGCTAGCACCTATTCTTAATAGTGC NaC-328,
CCAGGGCAGCTGCAAAATCAGAG
318 bp 54.2C

3Ax24.4 NaC-329 CCCGATGCGACCCAGTTTA, NaC-330,
TGGAGGGGTTTGATGCCATA
250 bp 55.2C

3Ax24.5 NaC-331 GATGGATGCCCTTCGAATACAGA, NaC-332,
TTCCCATTTAGTTTGTCAATAATC
258 bp 50.6C

3Ax24.6 NaC-321 AAGGGGAGGATTGACTTACCTAT, NaC-333,
TTGGCATGGACCTCCTCTTGA
302 bp 51.5C

Fig 6 (cont'd)

a. Asn43DEL:
9706 (allele 1; IGE patient): CAA GAT AAT GAT GAT GAG ;
9632 (allele 2; patient has IGE): CAA GAT --- GAT GAT GAG ;
allele 1 = 131/146 (0.90);
allele 2= 15/146 (0.10);
for IGE patients: homozygotes (22): 3958, 9632; heterozygotes (12): 9049, 9152, 9649, 9710, 9896, 10069, 10191, 10213, 9993, 10009, 10256 (note that 2 patients are homozygous for the rare allele; all patients have IGE); in controls: allele 1 = 45/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes found.

b. normal: tggtgtaaggtag,
10670 (IGE patient): tggtataaggtag

c. normal: ccccttatatctccaac,
10250 (IGE patient): ccccttatayctccaac;

d. Val1035Ile:
normal: AAA TAC GTA ATC GAT,
9269 (IGE patient): AAA TAC RTA ATC GAT; GTA>ATA = Val>Ile.

FIG - 7

SEQUENCE LISTING

<110> McGill University
Rouleau, Guy A.
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Cossette, Patrick
Ragsdale, David

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<140> PCT/CA00/01404
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Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
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Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu

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Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Gly
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Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
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Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser
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Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
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Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp
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245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
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Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu
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Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu
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Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp
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Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys

325 330 335

Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val
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Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly
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Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Arg Asp Ser Leu
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Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln
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Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu
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Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu
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Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro
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Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro
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Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro
755 760 765

Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe
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Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu
785 790 795 800

Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe
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Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly

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Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile
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Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val
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Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln
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Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val
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Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met
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Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met
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Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu
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Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu
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Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe Ile Arg
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Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp Leu Asn Asn
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Lys Lys Asp Ser Cys Met Ser Asn His Thr Ala Glu Ile Gly Lys Asp
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Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr Ser Gly Ile Gly Thr
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Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp Glu Ser Asp Tyr Met Ser
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Asp Leu Glu Glu Ser Lys Glu Lys Leu Asn Glu Ser Ser Ser Ser Ser
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Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Val Glu Glu Gln Pro Val
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Val Glu Pro Glu Glu Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly
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Cys Val Gln Arg Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg
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Gly Lys Gln Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu
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His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser
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Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile
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Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe Ile
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Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr Tyr Phe
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Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp Val Ser Leu
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Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu Leu Gly Ala Ile
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Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser
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Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Leu Gly Ala Ile
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Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile
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His Thr Asp Cys Leu Lys Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp
1395 1400 1405

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Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
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Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Glu Ser
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Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
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Val Gly Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro
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Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
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Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
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Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1665 1670 1675 1680

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
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Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
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Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
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Lys Val Asn Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
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Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
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Val Val Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
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Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
1795 1800 1805

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu
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Phe Glu Lys Leu Ser Gln Phe Ala Ala Ala Leu Glu Pro Pro Leu Asn
1825 1830 1835 1840

Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met
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Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr

1860 1865 1870

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
1875 1880 1885

Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln
1890 1895 1900

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val
1905 1910 1915 1920

Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys
1925 1930 1935

Gln Ala Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn
1940 1945 1950

Leu Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser
1955 1960 1965

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro Pro
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cataataaat gttaccatgg agcaaactaa attatctcca aaagccttca ttaggtagaa 180
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aactgaatca accactgttg tgttatattt aaacccatcc cttcttcaca tagttatgca 780
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tgaca 845

<210> 17
<211> 965
<212> DNA
<213> Homo sapiens

<400> 17
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taaaatgaga atgataatca aaaggaatga accatattct gttatgaatg ctgaaatctc 240
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<210> 18
<211> 641
<212> DNA
<213> Homo sapiens

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atgatacaat aagtcagaaa tatctgccat caccaattga atatgaaagt gcatgatgca 180
tgtgtttcat gaaattcact gtgtcaccat ttggttgttt gcttgtcata ttgctcaaat 240
taattgttta atgcattagc attttttttt acagggaaca accactgaaa ctgaaatgag 300
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gcaacgagca atgagtatag ccagcattct aacaaataca gtagaaggtt ggtaacaaat 420
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<210> 19
<211> 818
<212> DNA
<213> Homo sapiens

<400> 19
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tctgtaacaa aaatgtgttg attactgaaa ataagtttag tggatatgaa ataaatgtgt 240
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ttttcaggat ccagaagtag ctcatagatt aagaacat 818

<210> 20
<211> 645
<212> DNA
<213> Homo sapiens

<400> 20
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ttatctactt cgcgtttcca caaggataaa attaaataat gtatatgawa gtctttcatc 120
aactacaaat tgccatacaa atttaagtta gtaatagaat cattgtggga aaatagcata 180
agcattatgt tctaagagca aatcttatgt catgtatgtt attatctggt ggaattagat 240
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gttcatttcg attggtaaaa aaaaaaaaaa aaggaaccaa attcaaaaac ctttctaaca 480
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attaggttac cttagttcaa gggcwaggtc ggaaaggtaa cggtt 645

<210> 21
<211> 829
<212> DNA
<213> Homo sapiens

<400> 21
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aacgttaaat atgctaataa agatcatcgg caattccgtg ggggctctgg gaaatttaac 180
cctcgtcttg gccatcatcg tcttcatttt tgccgtggtc ggcatgcagc tctttggtaa 240
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ggtcatggtg attggaaacc tagcggtatg tacccactta agatatgcat tttggaaata 480
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caacacagca atatabcagt gcccctgcat tttttatacc aaattctatt ttgtcagtca 720
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<210> 22
<211> 909
<212> DNA
<213> Homo sapiens

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aattgctgtg gataggatgc acaaaggagt agcttatgtg aaaagaaaaa tatatgartt 480

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<211> 516
<212> DNA
<213> Homo sapiens

<400> 23
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aaattcatag taataatcct tcttggcagg caacttatta ccaaaattaa ggactttact 180
ttctatgtcc atctcactta cagaaactga atgaaagcag tagctcatca gaaggtagca 240
ctgtggacat cggcgcacct gtagaagaac agcccgtagt ggaacctgaa gaaactcttg 300
aacccgaagc ttgtttcact gaaggtaaag aaaagaatcc taatgttaat ctttcatttg 360
gagtgcagct tatttagctg ttggtcagct aanataaatc acatataata aaatngcact 420
ttgtaataga tataattcaa tcacctctaa tatnttgaca gacaaaaaaa cttaaagtct 480
agtgtcatgc tttgattata tctgcccaat atntgg 516

<210> 24
<211> 640
<212> DNA
<213> Homo sapiens

<400> 24
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actctaggct tagagagcta tgctagcaag acagagatga gcatagtaat aaaaagacaa 120
gacaaggaca ttgctaaagg atattatgga agcagagaca ctttatctac ttttatttca 180
acactttctg caggctgtgt acaaagattc aagtgttgtc aaatcaatgt ggaagaaggc 240
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gatttactct ataactctat atttctggat taacttttac tatgtatgta aatataattt 540
taagaagcta atcattaatt tttgcttact attaaatagc ccagaaagtg tagcccttca 600
gcttattcat taacaccaaa ggatgtgaat attcaattac 640

<210> 25
<211> 607

<212> DNA
<213> Homo sapiens

<400> 25
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tcatactttt ctttttcttc caccaatagt ctttcccctg attaaataag taaaagacct 120
ttgcgaggaa aaaaaaaaag taacagtaac tactgtttct ctgccctcct attccaatga 180
aatgtcatat gcatatgatt aatttttaa atagcttatg gagtataatt atttttgaaa 240
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gcttgtctta tttatattca aattctacaa tagtgagtct cagaccacta tgttatgttg 540
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gggctaa 607

<210> 26
<211> 336
<212> DNA
<213> Homo sapiens

<400> 26
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attgttatta ttcytgtgtg tgcaggtttc attggtcagt ttaacagcaa atgccttggg 120
ttactcagaa cttggagcct atcaatctct caggacacta agagctctga gacctctaag 180
agccttatct cgatttgaag ggatgagggt aagaaaaatg aaagaacctg aagtattgta 240
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gaatggcaaa ttcttgcaaa atgctcttta ttgttt 336

<210> 27
<211> 677
<212> DNA
<213> Homo sapiens

<400> 27
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tattacatgt aaggact 677

<210> 28
<211> 457
<212> DNA
<213> Homo sapiens

<400> 28
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gatcttacta agataattca acacatgaat tattttg 457

<210> 29
<211> 379
<212> DNA
<213> Homo sapiens

<400> 29
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tggtaggtgg aactccagcc taagtatgaa gaaagtctgt acatgtatct ttactttgtt 180
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ggagtatata ttataactg 379

<210> 30
<211> 393
<212> DNA
<213> Homo sapiens

<400> 30
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<210> 31
<211> 539
<212> DNA
<213> Homo sapiens

<400> 31
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tccattgtag gtaagaaata tttaaagttc ttaaattcag ttaaataaaa gtgaaagctg 480
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<210> 32
<211> 3403
<212> DNA
<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

<400> 35

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu
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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
        35                  40                  45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
    50                  55                  60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
65                  70                  75                  80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
                85                  90                  95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
            100                 105                 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
        115                 120                 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
    130                 135                 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
145                 150                 155                 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
                165                 170                 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
            180                 185                 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
        195                 200                 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
    210                 215                 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
225                 230                 235                 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
                245                 250                 255
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Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
            260                 265                 270

Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
        275                 280                 285

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
    290                 295                 300

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
305                 310                 315                 320

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
                325                 330                 335

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
            340                 345                 350

Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
        355                 360                 365

Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
    370                 375                 380

Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
385                 390                 395                 400

Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
                405                 410                 415

Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
            420                 425                 430

Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
        435                 440                 445

Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
    450                 455                 460

Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
465                 470                 475                 480

Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
                485                 490                 495

Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu
            500                 505                 510
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Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
    530                 535                 540

Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
                565                 570                 575

Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
    610                 615                 620

Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
625                 630                 635                 640

Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
                645                 650                 655

Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
            660                 665                 670

Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
        675                 680                 685

His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
    690                 695                 700

Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
705                 710                 715                 720

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
                725                 730                 735

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
            740                 745                 750

Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
        755                 760                 765
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Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
    770                 775                 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
785                 790                 795                 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
                805                 810                 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
            820                 825                 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
        835                 840                 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
    850                 855                 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
865                 870                 875                 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
                885                 890                 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
            900                 905                 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
        915                 920                 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
    930                 935                 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
945                 950                 955                 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
                965                 970                 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
            980                 985                 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
        995                1000                1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
   1010                1015                1020
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Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
1025 1030 1035 1040

Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
1045 1050 1055

Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
1060 1065 1070

Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
1075 1080 1085

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
1090 1095 1100

Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
1105 1110 1115 1120

Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
1125 1130 1135

Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
1140 1145 1150

Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
1155 1160 1165

Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
1170 1175 1180

Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
1185 1190 1195 1200

Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
1205 1210 1215

Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
1220 1225 1230

Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
1235 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
1250 1255 1260

Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu
1265 1270 1275 1280

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Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
                1285                1290                1295

Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
            1300                1305                1310

Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
        1315                1320                1325

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
    1330                1335                1340

Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
1345                1350                1355                1360

Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
                1365                1370                1375

Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
            1380                1385                1390

Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
        1395                1400                1405

Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
    1410                1415                1420

Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
1425                1430                1435                1440

Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
                1445                1450                1455

Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
            1460                1465                1470

Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
        1475                1480                1485

Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
    1490                1495                1500

Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
1505                1510                1515                1520

Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser
                1525                1530                1535
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Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
1540 1545 1550

Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
1555 1560 1565

Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
1570 1575 1580

Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
1585 1590 1595 1600

Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
1605 1610 1615

Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
1620 1625 1630

Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
1635 1640 1645

Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
1650 1655 1660

Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
1665 1670 1675 1680

Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
1685 1690 1695

Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
1700 1705 1710

Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
1730 1735 1740

Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
1745 1750 1755 1760

Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
1765 1770 1775

Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu
1780 1785 1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
1795 1800 1805

Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
1810 1815 1820

Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
1825 1830 1835 1840

Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
1845 1850 1855

Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
1860 1865 1870

Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
1875 1880 1885

Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
1890 1895 1900

Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
1905 1910 1915 1920

Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
1925 1930 1935

Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
1940 1945 1950

Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu
1970 1975 1980

Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
1985 1990 1995 2000

Arg Glu Ser Lys Lys
2005

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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
         35                  40                  45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
     50                  55                  60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
 65                  70                  75                  80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
                 85                  90                  95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
            100                 105                 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
        115                 120                 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
    130                 135                 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
145                 150                 155                 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
                165                 170                 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
            180                 185                 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
        195                 200                 205

Asn Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
    210                 215                 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
225                 230                 235                 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
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245 250 255

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
260 265 270

Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
275 280 285

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
290 295 300

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
305 310 315 320

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
325 330 335

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
340 345 350

Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
355 360 365

Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
370 375 380

Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
385 390 395 400

Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
405 410 415

Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
420 425 430

Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
435 440 445

Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
450 455 460

Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
465 470 475 480

Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
485 490 495

Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu

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            500                 505                 510

Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
    530                 535                 540

Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
                565                 570                 575

Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
    610                 615                 620

Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
625                 630                 635                 640

Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
                645                 650                 655

Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
            660                 665                 670

Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
        675                 680                 685

His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
    690                 695                 700

Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
705                 710                 715                 720

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
                725                 730                 735

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
            740                 745                 750

Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
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        755                 760                 765

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
    770                 775                 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
785                 790                 795                 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
                805                 810                 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
            820                 825                 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
        835                 840                 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
    850                 855                 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
865                 870                 875                 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
                885                 890                 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
            900                 905                 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
        915                 920                 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
    930                 935                 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
945                 950                 955                 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
                965                 970                 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
            980                 985                 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
        995                1000                1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
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1010 1015 1020

Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
1025 1030 1035 1040

Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
1045 1050 1055

Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
1060 1065 1070

Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
1075 1080 1085

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
1090 1095 1100

Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
1105 1110 1115 1120

Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
1125 1130 1135

Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
1140 1145 1150

Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
1155 1160 1165

Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
1170 1175 1180

Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
1185 1190 1195 1200

Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
1205 1210 1215

Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
1220 1225 1230

Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
1235 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
1250 1255 1260

Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu

1265 1270 1275 1280

Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
1285 1290 1295

Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
1300 1305 1310

Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
1315 1320 1325

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
1330 1335 1340

Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
1345 1350 1355 1360

Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
1365 1370 1375

Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
1380 1385 1390

Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
1395 1400 1405

Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
1410 1415 1420

Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
1425 1430 1435 1440

Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
1445 1450 1455

Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
1460 1465 1470

Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
1475 1480 1485

Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
1490 1495 1500

Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
1505 1510 1515 1520

Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser

1525 1530 1535

Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
1540 1545 1550

Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
1555 1560 1565

Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
1570 1575 1580

Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
1585 1590 1595 1600

Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
1605 1610 1615

Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
1620 1625 1630

Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
1635 1640 1645

Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
1650 1655 1660

Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
1665 1670 1675 1680

Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
1685 1690 1695

Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
1700 1705 1710

Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
1730 1735 1740

Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
1745 1750 1755 1760

Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
1765 1770 1775

Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu

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          1780                1785                1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
       1795                1800                1805

Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
   1810                1815                1820

Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
1825                1830                1835                1840

Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
               1845                1850                1855

Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
           1860                1865                1870

Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
       1875                1880                1885

Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
   1890                1895                1900

Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
1905                1910                1915                1920

Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
               1925                1930                1935

Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
           1940                1945                1950

Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
       1955                1960                1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu
   1970                1975                1980

Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
1985                1990                1995                2000

Arg Glu Ser Lys Lys
               2005
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<211> 912
<212> DNA

<213> Homo sapiens

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aaaagcctgt ggaagatcag ttccacaact gagagctttg ggctgcttca gacatatgtc 180
tgtgtgtacg ctgtgaaggt gtttctcttc acagttcccc gccctctagt ggtagttaca 240
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ccttttacag gaagttaggt gtggtctttg aaggagaatt aaaaaaaaaa aaaaaaaaaa 360
aaaaaagatt ttttttttt taaagcatga tggaatttta gctgcagtct tcttggggcc 420
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ttattatgct tattctctgt gatgcttctc tacctttaca gtagtagaat ccttggggaa 540
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gcattccata ta 912

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<211> 722
<212> DNA
<213> Homo sapiens

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ccttgctgct attgaacaac gcattgcaga agagaaagct aagagaccca aacaggaacg 240
caaggatgag gatgatgaaa atggcccaaa gccaaacagt gacttggaag cagsaaaatc 300
tcttccattt atttatggag acattcctcc agagatggtg tcagtgcccc tggaggatct 360
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tactaattgg ttctgggcta gtcccaggga tgatggtgaa gaaggctggc ctccttccct 480
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aa 722

<210> 39
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<212> DNA
<213> Homo sapiens

<400> 39

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tccaaaatat ctgtggttgg caatgttatg tgttctttct ttttctttcc ttttactcaa 480
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<211> 510
<212> DNA
<213> Homo sapiens

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atagtaagca ctaaagtttt aaacttcatg gtggtgaagg catggtagtg cataaaagta 180
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aaagaatgtg gagtaagtat aaatattttt caatattgac ctccctttat gtttcatatt 360
gtgcttttaa caccttgaga cctcctcaat ttctttaaca aatcatgcta gctactgtta 420
accagaccct gattcaaatt catttctgtc actaaatgtc ttctaggaca aagcttgtag 480
tgggctcact tagttgtgta aattactgca 510

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<211> 370
<212> DNA
<213> Homo sapiens

<400> 41
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caggtatacc tttacaggaa tttatacttt tgaatcactt attaaaatac ttgcaagggg 120
cttttgttta gaagatttca catttttacg ggatccatgg aattggttgg atttcacagt 180
cattactttt gcgtaagtat cttaatacat tttctatcct ggaagagtaa atcactggtg 240
ggagcctata ctatattttc cttggtggct tgccttgaca gaccaagcat ttntcttagt 300
aatcatagtt ttcttccaat caaattatcc agtttggaga aattaggaac tatcatagta 360
aattacatgg 370

<210> 42
<211> 370
<212> DNA
<213> Homo sapiens

<400> 42
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atgaaagacc aangaagacg tagatttccc taaattctga ataactctga tttaattcta 180
caggtatgta acagaatttg taaacctagg caatgtttca gctcttcgaa ctttcagagt 240
cttgagagct ttgaaaacta tttctgtaat tccaggtaag aagaaaatgg tataaggtgg 300
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cctattacag 370

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<211> 410
<212> DNA
<213> Homo sapiens

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ggcaatgtct cagcgttgag aacattcaga gttctccgag cattgaaaac aatttcagtc 180
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gcaagaattg gtacatcatt ttttggatgg atttgattct ttgcttttta cccgttgctt 360
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<211> 1066
<212> DNA
<213> Homo sapiens

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tcacaaacat taaactaata ttgttggcat tctgcatgac atttttattt tccaggccaa 180
gctcatgata tttttgccgg taaaatagct gttgagtagt atatttaant tccccccttct 240
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agagatatca aaggatacct tattctattt ttsttatctg tccattgata tagtaaaagt 720
tctcatttga aaatgtgttg tcttatactc atgttgaaag taatttcata ttatgccata 780
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taatttggcc ctatttggtt gatgcaacat atgtattgag tacatatgct atatctgaaa 960

ctagagaaac catttatcaa gatgaaataa gaatttgtgt gctcctcaga aggttaagta 1020
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<211> 385
<212> DNA
<213> Homo sapiens

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gattttaatg attctttcta ttcctttctc tttaaatagg tcacttttat tttttacagg 180
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tgaccaggat aagtgtagat tctca 385

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<211> 430
<212> DNA
<213> Homo sapiens

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gctttttttct agtgcctgta taaaacagac attggcatat attaaaacag gaaaaccaat 180
tagcagactt gccgttattg actycctctc tttcctctaa cctaattaca gccagtgtcc 240
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tcaagagaat 430

<210> 47
<211> 646
<212> DNA
<213> Homo sapiens

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<211> 711
<212> DNA
<213> Homo sapiens

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tgaagctcaa ttaagcagta acatgataat tatttttttaa gatnatatgc aacttcccac 180
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<211> 1026
<212> DNA
<213> Homo sapiens

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aggaga 1026

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<211> 601
<212> DNA
<213> Homo sapiens

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<211> 645
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 52

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 615
<212> DNA
<213> Homo sapiens

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<211> 400
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<213> Homo sapiens

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<211> 560
<212> DNA
<213> Homo sapiens

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ccaatttaaa tacatataca 560

<210> 58
<211> 480
<212> DNA
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<211> 640
<212> DNA
<213> Homo sapiens

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<210> 60
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<213> Homo sapiens

<400> 60
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<211> 366
<212> DNA
<213> Homo sapiens

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<211> 560
<212> DNA
<213> Homo sapiens

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<210> 63
<211> 650
<212> DNA
<213> Homo sapiens

<400> 63
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<211> 3700
<212> DNA
<213> Homo sapiens

<400> 64
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<211> 9112
<212> DNA
<213> Homo sapiens

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ctatcactaa tgcatgttaa tattgcctat gctgctctat tttactcaat ccattcttca 7620
caagtcttgg ttaaagaatg tcacatattg gtgatagaat gaattcaacc tgctctgtcc 7680
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caattccaaa cttttgaatc cataagattt ttcaatggat aatttcctaa aataaaagtt 8040
agataatggg ttttatggat ttctttgtta taatatattt tctaccattc caataggaga 8100
tacattggtc aaacactcaa acctagatca ttttctacca actatggttg cctcaatata 8160
acctttttatt catagatgtt ttttttttatt caacttttgt agtatttacg tatgcagact 8220
agtcttattt ttttaattcc tgctgcacta aagctattac aaatataaca tggactttgt 8280
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tgttttttgc acaaaccaaa agtttaatgt taattctttt tacaaaacta tttactgtag 8400
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ttattgagcc aaaagaataa atttcatttt ttattgcatt tcacttattg gcctctgggg 8520
ttttttgttt ttgttttttg ctgttggcag tttaaaatat atataattaa taaaacctgt 8580
gcttgatctg acatttgtat acataaaagt ttacatgaat tttacaacag actagtgcat 8640
gattcaccaa gcagtactac agaacaaagg caaatgaaaa gcagctttgt gcacttttat 8700
gtgtgcaaag gatcaagttc acatgttcca actttcaggt ttgataataa tagtagtaac 8760
cacctacaat agctttcaat ttcaattaac tcccttggct ataagcatct aaactcatct 8820
tctttcaata taattgatgc tatctcctaa ttacttggtg gctaataaat gttacattct 8880
ttgttactta aatgcattat ataaactcct atgtatacat aaggtattaa tgatatagtt 8940
attgagaatt tatattaact ttttttttcaa gaacccttgg atttatgtga ggtcaaaacc 9000
aaactcttat tctcagtgga aaactccagt tgtaatgcat atttttaaag acaatttgga 9060
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<211> 1951
<212> PRT
<213> Homo sapiens

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Ala Ala Glu Glu
20 25 30

Lys Ala Lys Lys Pro Lys Lys Glu Gln Asp Asn Asp Asp Glu Asn Lys
35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
50 55 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
85 90 95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
100 105 110

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Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
        115                 120                 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
    130                 135                 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145                 150                 155                 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala Arg
                165                 170                 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
            180                 185                 190

Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Asp
        195                 200                 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
    210                 215                 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225                 230                 235                 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
                245                 250                 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
            260                 265                 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
        275                 280                 285

Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
    290                 295                 300

Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
305                 310                 315                 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
                325                 330                 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
            340                 345                 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
        355                 360                 365
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Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
    370                 375                 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
385                 390                 395                 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
                405                 410                 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
            420                 425                 430

Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
        435                 440                 445

Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
    450                 455                 460

Ala Ser Ala Ala Ser Arg Asp Phe Ser Gly Ile Gly Gly Leu Gly Glu
465                 470                 475                 480

Leu Leu Glu Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala
                485                 490                 495

Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
            500                 505                 510

Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
    530                 535                 540

Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
                565                 570                 575

Ile Phe Ser Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
    610                 615                 620
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Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
625                 630                 635                 640

Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
                645                 650                 655

Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
            660                 665                 670

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
        675                 680                 685

Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
    690                 695                 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
705                 710                 715                 720

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
                725                 730                 735

Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
            740                 745                 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
        755                 760                 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
    770                 775                 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
785                 790                 795                 800

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
                805                 810                 815

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
            820                 825                 830

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
        835                 840                 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
    850                 855                 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
865                 870                 875                 880
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Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
                885                 890                 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
            900                 905                 910

Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
        915                 920                 925

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
    930                 935                 940

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
945                 950                 955                 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
                965                 970                 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
            980                 985                 990

Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
        995                1000                1005

Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
   1010                1015                1020

Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
1025                1030                1035                1040

Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
                1045                1050                1055

Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
            1060                1065                1070

Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
        1075                1080                1085

Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu
   1090                1095                1100

Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe
1105                1110                1115                1120

Thr Glu Gly Cys Ile Lys Lys Phe Pro Phe Cys Gln Val Ser Thr Glu
                1125                1130                1135
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Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser
1140 1145 1150

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu
1155 1160 1165

Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg
1170 1175 1180

Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr
1185 1190 1195 1200

Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Phe Gln
1205 1210 1215

Thr Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp
1220 1225 1230

Val Ser Leu Val Ser Leu Val Ala Asn Ala Leu Gly Tyr Ser Glu Leu
1235 1240 1245

Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg
1250 1255 1260

Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Val
1265 1270 1275 1280

Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe
1285 1290 1295

Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
1300 1305 1310

Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
1315 1320 1325

Val Asn Asn Leu Ser Asp Cys Gln Ala Leu Gly Lys Gln Ala Arg Trp
1330 1335 1340

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
1345 1350 1355 1360

Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
1365 1370 1375

Ala Val Asp Ser Arg Asp Val Lys Leu Gln Pro Val Tyr Glu Glu Asn
1380 1385 1390

Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
1395 1400 1405

Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
1410 1415 1420

Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
1425 1430 1435 1440

Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
1445 1450 1455

Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
1460 1465 1470

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
1475 1480 1485

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
1490 1495 1500

Met Thr Leu Val Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
1505 1510 1515 1520

Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
1525 1530 1535

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
1540 1545 1550

Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
1555 1560 1565

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
1570 1575 1580

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
1585 1590 1595 1600

Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1605 1610 1615

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
1620 1625 1630

Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
1635 1640 1645

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
1650 1655 1660

Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
1665 1670 1675 1680

Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
1685 1690 1695

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
1700 1705 1710

Val Val Asn Ser Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
1715 1720 1725

Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
1730 1735 1740

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
1745 1750 1755 1760

Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
1765 1770 1775

Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
1780 1785 1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
1795 1800 1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
1810 1815 1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
1825 1830 1835 1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
1845 1850 1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
1860 1865 1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
1875 1880 1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
1890 1895 1900

Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
1905 1910 1915 1920

Tyr Asp Ser Val Thr Lys Pro Asp Lys Glu Lys Phe Glu Lys Asp Lys
1925 1930 1935

Pro Glu Lys Glu Ser Lys Gly Lys Glu Val Arg Glu Asn Gln Lys
1940 1945 1950

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<211> 1951
<212> PRT
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Met Ala Gln Ala Leu Leu Val Pro Pro Gly Pro Glu Ser Phe Arg Leu
1 5 10 15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Ala Ala Glu Glu
20 25 30

Lys Ala Lys Lys Pro Lys Lys Glu Gln Asp Asn Asp Asp Glu Asn Lys
35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
50 55 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
85 90 95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
100 105 110

Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
130 135 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala Arg
165 170 175

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Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
            180                 185                 190

Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Ser
        195                 200                 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
    210                 215                 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225                 230                 235                 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
                245                 250                 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
            260                 265                 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
        275                 280                 285

Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
    290                 295                 300

Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
305                 310                 315                 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
                325                 330                 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
            340                 345                 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
        355                 360                 365

Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
    370                 375                 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
385                 390                 395                 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
                405                 410                 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
            420                 425                 430
```

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Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
        435                 440                 445

Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
    450                 455                 460

Ala Ser Ala Ala Ser Arg Asp Phe Ser Gly Ile Gly Gly Leu Gly Glu
465                 470                 475                 480

Leu Leu Glu Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala
                485                 490                 495

Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
            500                 505                 510

Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
    530                 535                 540

Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
                565                 570                 575

Ile Phe Ser Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
    610                 615                 620

Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
625                 630                 635                 640

Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
                645                 650                 655

Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
            660                 665                 670

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
        675                 680                 685
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Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
    690                 695                 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
705                 710                 715                 720

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
                725                 730                 735

Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
            740                 745                 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
        755                 760                 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
    770                 775                 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
785                 790                 795                 800

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
                805                 810                 815

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
            820                 825                 830

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
        835                 840                 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
    850                 855                 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
865                 870                 875                 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
                885                 890                 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
            900                 905                 910

Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
        915                 920                 925

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
    930                 935                 940
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Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
945                 950                 955                 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
                965                 970                 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
            980                 985                 990

Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
        995                1000                1005

Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
   1010                1015                1020

Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
1025                1030                1035                1040

Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
                1045                1050                1055

Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
            1060                1065                1070

Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
       1075                1080                1085

Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu
   1090                1095                1100

Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe
1105                1110                1115                1120

Thr Glu Gly Cys Ile Lys Lys Phe Pro Phe Cys Gln Val Ser Thr Glu
                1125                1130                1135

Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser
            1140                1145                1150

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu
       1155                1160                1165

Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg
   1170                1175                1180

Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr
1185                1190                1195                1200
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Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Phe Gln
                1205                1210                1215

Thr Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp
            1220                1225                1230

Val Ser Leu Val Ser Leu Val Ala Asn Ala Leu Gly Tyr Ser Glu Leu
        1235                1240                1245

Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg
    1250                1255                1260

Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Val
1265                1270                1275                1280

Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe
                1285                1290                1295

Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
            1300                1305                1310

Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
        1315                1320                1325

Val Asn Asn Leu Ser Asp Cys Gln Ala Leu Gly Lys Gln Ala Arg Trp
    1330                1335                1340

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
1345                1350                1355                1360

Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
                1365                1370                1375

Ala Val Asp Ser Arg Asp Val Lys Leu Gln Pro Val Tyr Glu Glu Asn
            1380                1385                1390

Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
        1395                1400                1405

Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
    1410                1415                1420

Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
1425                1430                1435                1440

Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
                1445                1450                1455
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Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
1460 1465 1470

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
1475 1480 1485

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
1490 1495 1500

Met Thr Leu Val Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
1505 1510 1515 1520

Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
1525 1530 1535

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
1540 1545 1550

Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
1555 1560 1565

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
1570 1575 1580

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
1585 1590 1595 1600

Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1605 1610 1615

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
1620 1625 1630

Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
1635 1640 1645

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
1650 1655 1660

Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
1665 1670 1675 1680

Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
1685 1690 1695

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
1700 1705 1710

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Val Val Asn Ser Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
       1715                1720                1725

Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
   1730                1735                1740

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
1745                1750                1755                1760

Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
               1765                1770                1775

Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
           1780                1785                1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
       1795                1800                1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
   1810                1815                1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
1825                1830                1835                1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
               1845                1850                1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
           1860                1865                1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
       1875                1880                1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
   1890                1895                1900

Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
1905                1910                1915                1920

Tyr Asp Ser Val Thr Lys Pro Asp Lys Glu Lys Phe Glu Lys Asp Lys
               1925                1930                1935

Pro Glu Lys Glu Ser Lys Gly Lys Glu Val Arg Glu Asn Gln Lys
           1940                1945                1950
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<212> DNA
<213> Homo sapiens

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<212> DNA
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ataaaattat gtaagaactc tgtataataa gctcacagag tacaagaaag gagaggaaaa 180
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<210> 72
<211> 1025
<212> DNA
<213> Homo sapiens

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atttttatca caatataata aaacaaacat ttataagaaa tgaagtcaag agttggttac 960
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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atttataaat ggccatggta acctactaac atttattcct taactataat ctactttatt 180
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<210> 75
<211> 701
<212> DNA
<213> Homo sapiens

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<211> 286
<212> DNA
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<400> 76
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<211> 515
<212> DNA
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<211> 564
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 501
<212> DNA
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<210> 81
<211> 432
<212> DNA
<213> Homo sapiens

<400> 81
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<212> DNA
<213> Homo sapiens

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<210> 84
<211> 566
<212> DNA

<213> Homo sapiens

<400> 84
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<211> 664
<212> DNA
<213> Homo sapiens

<400> 86
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<211> 750
<212> DNA
<213> Homo sapiens

<400> 87
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cacatgaacg acttcttcca ctccttcctg attgtgttcc gcgtgctgtg tggagagtgg 480
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agaacaagag cagacagtag ctaggaacgt ggccagatgt agtaaacata tctctggttt 660
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aacttctcct gggctctggt ttcccatttt 750

<210> 88
<211> 768
<212> DNA
<213> Homo sapiens

<400> 88
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ttttaggctg ttatttaaat gcatatttca atattaarat aggcattttt ctttttttct 180
tttaggttct gaacctcttt ctggccttat tgttgagttc atttagctca gacaaccttg 240
ctgctactga tgatgacaat gaaatgaata atctgcagat tgcagtagga agaatgcaaa 300
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gtgtaggtac tggaagcagt gttgaaaaat acgtaatcga tgaaaatgat tatatgtcat 540
tcataaacaa ccccagcctc accgtcacag tgccaattgc tgttggagag tctgactttg 600
aaaacttaaa tactgaagag ttcagcagtg agtcagaact agaagaaagc aaggaggtaa 660
ggaatgcttt taaatttttt gttccatttc ctatgataac catgtactac agttatttac 720
tattttcatt gtgcttatat gcattatcga aaagcaatga ttgtaagt 768

<210> 89
<211> 471
<212> DNA
<213> Homo sapiens

<400> 89
taattattag tacataatga tcagtaatgc taatagagtt aaatgctatc actacatttt 60
ttttcacaca atgacacagt atttcccagt tagttaaata aaaggggaa aatcacatct 120
ttgaaatggg attttgtttc cagaaattaa atgcaaccag ctcatctgaa ggaagcacag 180
ttgatgttgt tctaccccga gaaggtgaac aagctgaaac tgaacccgaa gaagacctta 240
aaccggaagc ttgttttact gaaggtaaac aagctctgat gtgattaaat acaatctccc 300
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gtggtggctt atgcctgtaa ccccaaaatt ttgggaggct acggtaggag gattgcttga 420
ccccaggagt ttgagaccac cctgggaaat gtagtaaggc tttgcctcta c 471

<210> 90
<211> 623
<212> DNA
<213> Homo sapiens

<400> 90
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gagtggggaa ggggcaagaa agtttatttt ttcctattta agattaaaat atatttttta 180
attaactata tttsattttt aggatgtatt aaaaagtttc cattctgtca agtaagtaca 240
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cagatgcaaa cactgagctt cagaatcaaa agaaaaggca tatctgtgtc ttgcagagct 480
tggcacccaa ggtttaacga tgcaaaattc agttctgaac aaatcagcac catgaaacag 540
ccagatggaa tttctcatct ggtgtttatc taacagatgt tttcctcact gagacaacca 600
tttgcagaga cattctgtaa cca 623

<210> 91
<211> 520
<212> DNA
<213> Homo sapiens

<400> 91
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ccatttaagt aaaataaaat atttttgatt cataggcctt tgaagatata tacattgaac 180
agcgaaagac tatcaaaacc atgctagaat atgctgacaa agtctttacc tatatattca 240
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tttttaaaag aggcaagtt gacatttcat atgtttctgt tattaaaact ttcactaata 420
atgacataat tatgcagtta tttaaacaaa actgtaacat atgcaacaat gaggaatatc 480
tcatgggaaa gagtagagga ggtcctaaac atgggcagtg 520

<210> 92
<211> 595
<212> DNA
<213> Homo sapiens

<400> 92
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atcagtggta tatgcacaag ttgaaaaggg gtccatggta taaaatatct aactggagat 120
attgacacgt gttgataaat atgggcaagt attctggttt cattggttaa aaaaaagcaa 180
tagtatgaga tgagactggc aatataagat gaccccacta tgtggaagat gaaagttgcc 240
aaggtatgtc caaattagta tttagtctgc attaaataga taccacaccc tataccttca 300
gtcaacagtt tatttcttgg tgaactaatt aatttttttt tccttttgta ggtttctttg 360
gttagcctgg tagccaatgc tcttggctac tcagaactcg gtgccatcaa atcattacgg 420
acattaagag ctttaagacc tctaagagcc ttatcccggt ttgaaggcat gagggtaaga 480
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aagggtgcca tactcttctg atatttattt caatagaaat tacagaatta gaagc 595

<210> 93
<211> 787
<212> DNA
<213> Homo sapiens

<400> 93
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ttttccttca aatatgtgct agaaaaatta gaagaaacaa cttgtccacc tagattttta 180
tttaactctt ttcaagcaca tattaatact aaacaaatac attgaaggaa tggtttccat 240
tcaaaaggtt tgtaagctat gttcccctcg ctgtctcttc taggtggttg tgaatgctct 300
tgttggagca attccctcta tcatgaatgt gctgttggtc tgtctcatct tctggttgat 360
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tgcactgctt caagtggtaa gtggctactg tacgagtttt gaaaaagttt tcaagatgtt 600
tcaaggaaga ttatttccct gatgttcttc gtttgaatga ctaacatttg acagcatgaa 660
aaaaagttaa tgataacacc tataatatca gcttgaattg atcataaaaa agatgttaca 720
attattttat aatgtatttt ccttagtgtt aagcttttag tatgttttaa tgtgatttta 780
tatttct 787

<210> 94
<211> 438

<212> DNA
<213> Homo sapiens

<400> 94
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ctcttgatat gaaatttcac aatattgtac aaaaagttat ttgttataat actgtcagat 120
tttcatctgg ttaaatgtca ttgttaggtg aaatttttat gaacaattca aatatatgtt 180
atttacaggc cacatttaaa ggctggatgg atattatgta tgcagctgtt gattcacgag 240
atgtaagtat cactcaaata ttatttatag gttctagatt tcttatggtg aatattggtg 300
gtaatttaaa cactgataca tccaaaattc tatattagaa catttaatat tgcatataaa 360
aaatgaacag tctgcttcaa tatagatgat gcttgattaa tgtgtgccta atatacaata 420
tgtagctaat atgaaacg 438

<210> 95
<211> 637
<212> DNA
<213> Homo sapiens

<400> 95
gtaaggcaca atgggaaaag agaatcaaga acaatcataa aacttgcaaa ccttcatttt 60
actagatcat actagtttta aaaaattgtt tttgtagaac aatatctcag ggtaaggcaa 120
aagtagcact gtattaagta acagcactca ataaattact gatttagtgt aagtatttat 180
agtatttttc atattattta atattttcaa tatcatttag gttaaacttc agcctgtata 240
tgaagaaaat ctgtacatgt atttatactt tgtcatcttt atcatctttg ggtcattctt 300
cactctgaat ctattcattg gtgtcatcat agataacttc aaccagcaga aaaagaagat 360
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tctccagtgc tttagcttgg cttacagagc ctttcag 637

<210> 96
<211> 637
<212> DNA
<213> Homo sapiens

<400> 96
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aagcaggata aatgtatatg taggaggata atatccactt aaaaattaga aaagattaaa 180
ggaaagacaa atatttttg tgaaagtact attggaacac agaattgtaa ccagttttat 240
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aagaattact tgtctccttt aatgttccaa agccatgcgt ccatatggtc aaattgagca 420
atgctctgga gcagaacata ttaggtgata tcaccaatat tgagccctaa ttataaagtt 480
catattttgc atcataattc acaacttctg cactcattag gagttaccac attccaaaaa 540

aaggaggtaa tgttctttat aatttgtgag ttgaaaactt ctagctcagg gttcctaata 600
aatacttcca aagcaaggtt cactttcctg ctaccaa 637

<210> 97
<211> 759
<212> DNA
<213> Homo sapiens

<400> 97
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gaagagaaaa aaagcacaca aaattgtttg gggtaatatg aggagggtgc acatccatcc 120
cgtatgtgga agggctttat ctacaatttt actgcattat tctttatgaa atatatatag 180
taaccttatt tctcttctct cactttctag aacaaattcc aaggaatggt ctttgatttt 240
gtaaccagac aagtctttga tatcagcatc atgatcctca tctgcctcaa catggtcacc 300
atgatggtgg aaacggatga ccagggcaaa tacatgaccc tagttttgtc ccggatcaac 360
ctagtgttca ttgttctgtt cactggagaa tttgtgctga agctcgtctc cctcagacac 420
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aacactagca tatttgaata aaaactctga aacctgggtt tattcacaaa gctaactagt 660
tagaaaccat gttaggaata ccagatttgg gaaagaggtg aagaagacag gaaataaaca 720
ttatcaggta ctctcctaat cttaaaccaa ggtcacagg 759

<210> 98
<211> 3975
<212> DNA
<213> Homo sapiens

<400> 98
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caagtttgtt gtgttcatag accttaaaaa agataaagcc atcatgtaaa gtgaaaagat 120
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atataaggtg gctaa 3975

<210> 99
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 99
tgtgttctgc cccagtgaga ct 22

<210> 100
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 100
cttcctgctc tgcccaaact gaat 24

<210> 101
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 101
ggcgatgtaa tgtaaggtgc tgtc 24

<210> 102
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 102
gtgccttcag ttgcaattgt tcag 24

<210> 103
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 103
ttaggaattt catatgcaga ataa 24

<210> 104
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 104
tgggccattt ttcgtcgtc 19

<210> 105
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 105
gaaagacgca ttgcagaaga aaagg 25

<210> 106

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 106
ctattggcat gtgttggtgc taca 24

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 107
gtgctggttt ctcatttaac tttac 25

<210> 108
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 108
ttcccaactt aatttgatat ttagc 25

<210> 109
<211> 24
<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 109

gcagtttggg cttttcaatg ttag 24

<210> 110
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 110
gacacagttt caraatcccr aatg 24

<210> 111
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 111
ttagggctac gtttcatttg tatg 24

<210> 112
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 112
agcactgatg gaaaaccaaa ctat 24

<210> 113
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 113
agcccatgca gtaatataaa tcct 24

<210> 114
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 114
tccaggctga taagctatgt ctaa 24

<210> 115
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 115
ctgtggcctg cctgagcgta tt 22

<210> 116
<211> 24
<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 116
ccaattctac tttttaagga aatg 24

<210> 117
<211> 19

<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 117
aaatacttgt gcctttgaa 19

<210> 118
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 118
gtacatacaa tatacacaga tgc 23

<210> 119
<211> 23
<212> DNA
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<220>
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<400> 119
aggcagcaga acgacttgta ata 23

<210> 120
<211> 24
<212> DNA
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<220>
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<400> 120
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<210> 121
<211> 24
<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 121
gttgagcacc cttagtgaat aata 24

<210> 122
<211> 24
<212> DNA
<213> Artificial Sequence

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<400> 377

caaacgaaga acatcaggga aata 24

<210> 378
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<400> 378
ttcacaatat tgtacaaaaa gtta 24

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<400> 379
attaccacca atattcacca taag 24

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cccgtatgtg gaagggcttt at 22

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<210> 391
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<400> 391
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oligonucleotide

<400> 392
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cccgatgcga cccagttta 19

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tggaggggtt tgatgccata 20

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<210> 398
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<210> 399
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<213> Homo sapiens

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<400> 401
caagatgatg atgag 15

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<400> 404
ccccttatat ctccaac 17

<210> 405
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<212> DNA
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<400> 405
ccccttatay ctccaac 17

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<400> 406
aaatacgtaa tcgat 15

<210> 407
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aaatacataa tcgat 15

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aaatacrtaa tcgat 15